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(71) Applicant *(for all designated States except US)*: **NU-FARM LIMITED** [NZ/NZ]; 103-105 Pipe Road, Laverton North, Victoria 3026 (AU).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **SORENSEN, Allen, Paul** [NZ/NZ]; 6A Rapaki Place, Te Atatu North, Auckland (NZ). **VICKERS, Mark, Colin** [NZ/NZ]; 23 Meadowland Drive, Howick, Auckland (NZ).

(74) Agents: **CALHOUN, Douglas, C. et al.**; A J Park, 6th Floor, Huddart Parker Building, Post Office Square, P.O. Box 949, Wellington 6015 (NZ).

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(54) Title: STABLE BIOCIDAL COMPOSITIONS

(57) Abstract: A partitioned (preferably biocidal) composition comprising, in a first liquid phase (preferably organic) a first active ingredient (preferably biocidal), and, in a second liquid phase (preferably aqueous at acid pH), a second active ingredient (preferably biocidal), said active ingredient in said first liquid phase being unstable chemically in the conditions of said second liquid phase. Optionally particles may be suspended in at least in the preferred acqueous phase and preferaly said particles are themselves biocidal. The composition enables a chemically and physically stable anthelmintic composition to be prepared of at least two incompatible anthelmintic actives (viz. A macrocyclic lactone (eg; ivermectin), and levamisole) and preferably at least a third anthelmintic active (eg; a benzimidazole (eg; albendazole)).

STABLE BIOCIDAL COMPOSITIONS

The present invention relates to pesticidal compositions, their preparation and their use.

More particularly the present invention relates to multiple active ingredient liquid formulations of a kind where for stability purposes different environments are required for at least two of the active ingredients. For instance, when in an aqueous phase pH requirements for stability differ significantly, eg; a low pH is required for levamisole and a neutral pH is required for abamectin, a macrocyclic lactone (ML) (see Table 2 hereafter). Also of the common anthelmintics, levamisole salts are usually much more soluble than morantel salts in aqueous systems, M.L anthelmintics are generally more soluble in organic systems than aqueous systems and benzimidazoles are sparingly soluble.

A particular (but not only) area of interest in stable formulation are those formulations of biocides useful in controlling helminths including nematodes, cestodes, trematodes, and/or ectoparasites. In this respect the mode of administration including oral, injectable or pour-on (transdermal) routes of such a formulation (whether after aqueous dilution or not) is not critical to the invention.

It is known that simultaneous administration of levamisole and mebendazole [E M Bennet, C Behm, and C Bryant, Int J Parasitology, 1978, 8, 463-466] enhances the anthelmintic activity of benzimidazoles. New Zealand Patent 208288 discloses compositions which contain levamisole and at least one substituted benzimidazole carbamate.

It is also known, based on mathematical modelling that combining 3 or more actives that act to kill a pest in different ways reduces the risk of parasite developing resistance to each of the individual actives if used separately and on their own.

It is also known that it is desirable for ease of use that these actives are combined together in one stable formulation so that administration is by one single administration of an oral, injectable, parenteral or pour-on formulation. It is also desirable that this combined formulation is sufficiently stable so that it can be stored and the formulation used or reused at a later date without degradation of the actives or significant physical changes to the formulations.

Anderson et al in "Mixtures of Anthelmintics: A Strategy Against Resistance" Australian Veterinary Journal, Vol 65, No.2, February 1988, Pages 62-64 suggested that where multiple resistance to broad spectrum nematocides had arisen, treatment with mixtures of nematocides provided effective control of the nematode infections sufficient for use in

resistance preventative programs. Hence the need now, much later than 1988, for combined active formulations.

Ancare New Zealand Limited formulated a double active anthelmintic of levamisole and niclosamide in paraffin oil (LEVITAPE™) to target both tapeworm and roundworm found any water contamination rendered the product too viscous to use. They tried PEG 6000 wax encasement of niclosamide to protect it from water to no avail. They even tried a detergent based mixture of niclosamide and levamisole but whilst stable it was not safe nor easy to use as a oral drench.

Ancare found that combining benzimidazole drenches with levamisole drenches results in an unstable product due to the different pH values needed to maintain the stability of the individual products. Often, on standing for an hour or two the drenches separate out with the levamisole on top and the benzimidazole left as a sludge on the bottom. It these are not thoroughly mixed again before use the animal may be under or overdosed. A possible consequence of underdosing with the benzimidazole is the build up of a parasite resistant to the benzimidazole.

Merck NZ 183847 discloses avermectin anthelmintic compounds for parenteral administration where they may be carried by a vegetable oil such as peanut oil, cotton seed oil and the like.

Sankyo NZ 199817 refers to oral formulations of two or more anthelmintics where one is a macrolide (or ML) anthelmintic and another may be, for example, a benzimidazole (eg; albendazole), a salicylamide (eg; niclosamide) or an isoquinoline compound (eg; praziquantel). Such formulations are not exemplified by any storage stable formulation although reference is made to formulation as an aqueous solution, as a solution in another suitable non-toxic solvent or as a suspension or dispersion incorporating a suspension aid and a wetting agent (eg; bentonite) or other constituents.

Doramectin is available from Pfizer as DECTOMAX™ as a parenteral formulation of sesame oil and ethyl oleate.

Ashmont NZ 280085/280134 discloses injectable ML anthelmintic formulations (eg; abamectin or ivermectin) where a alcohol (such as benzyl alcohol - long since used as a preservative in injectable formulations) acts as a co-solvent with a vegetable oil vehicle (eg; soyabean oil, sesame oil or corn oil). The optional inclusion of ethyl oleate is also disclosed.

Ashmont further discloses (w/w %) a formulation as follows;

ML anthelmintic active 0.5 to 5% w/w

benzyl alcohol	1 to 30% w/w
vegetable oil	to 100% w/w
ethyl oleate	zero or 5 to 30% w/w

Despite combinations above being developed no stable ML anthelmintic and levamisole combination has been marketed. Previous attempts at such a combination resulted in unstable formulation - see our own Examples 1 - 6 hereafter.

The present invention is directed to compositions having at least two actives preferably each usable as an anthelmintic active (albeit with a different spectrum of efficacy with respect to nematodes, trematodes, flukes, etc.) and preferably involving other therapeutic agents.

In another aspect the present invention relates to a benzimidazole containing composition (eg; for pour-on use) where the benzimidazole is solubilised in an organic acid containing phase (eg; lactic acid).

As used herein the term "anthelmintic" and derivatives thereof shall encompass, where the context allows any one or more of a nematocidal, trematocidal and cestocidal active compounds. Where the context so allows "pesticidal" and derivatives thereof shall include any such anthelmintic and any ectoparasitocidal compound. Where the context allows "ectoparasitocidal" shall include compounds effective against any one or more of ticks, lice, flies, et al.

As used herein the term "stable" means at least 3 months (preferably at least 18 months) chemical stability (eg; within plus or minus 10% $^{w}/_{w}$ of its stated composition) of the active ingredients when stored at 25°C or below and at ambient humidity and of reasonable physical stability such that the composition is substantially homogeneous (despite any option particulate inclusion(s)) and/or can readily be agitated to such condition.

As used herein the term "particle", "particles" and "particulate" means true particles (ie; parts of solids) as well as liposomes or the equivalent optionally which may be or carry an active ingredient. Preferably said particles are almost exclusively less than 100μ (microns). Ideally the smaller the better (eg; preferably substantially all less than 50μ, more preferably less than 30μ, still more preferably than 20μ and even more preferably less than 10μ).

As used herein the term "solubility" refers to the ability of a compound to be dissolved in a specific phase.

As used herein "lipophilic" means a greater tendency to an orangic, oil or the like phase as opposed to the other phase (preferably aqueous).

As referred to herein the term "pourable" or "flowable" in respect of a fluid or liquid covers viscosities ranging from a free flowing liquid to a gel or paste consistency that is able to be expelled by syringe, drench or paste gun. The term "pourable" is irrespective of whether it is to be used as a pour on or otherwise.

In a first aspect the invention consists in **a pesticidal composition** comprising or including

(i) at least one active ingredient that is lipophilic in character,

(ii) at least one organic liquid carrier which carries at least most of the lipophilic active ingredient(s), thereby defining an organic liquid phase,

(iii) levamisole, and

(iv) at least water which carries at least most of said levamisole thereby defining an aqueous phase,

wherein said aqueous phase has a pH of less than 7,

and wherein there is present in said aqueous phase an emulsifying agent or agents,

and wherein said phases exist in, or can be shaken or agitated into, the form of an emulsion with said particulate content, if any, at least substantially present in the aqueous phase.

Preferably said pesticidal composition (or indeed any biocidal composition) disclosed herein is a veterinary composition.

Preferably the lipophilic active ingredient is chosen from the class of macro cyclic lactones (hereafter "ML").

Preferably there is present in said aqueous phase a particulate content.

Ideally said aqueous phase has a pH of less than 6 (more preferably less than 5 and most preferably 4 or below).

Preferably said aqueous phase includes a buffering system to buffer the pH to preferably a pH suitable for the levamisole.

Preferably said buffering system is a citric acid/citrate salt system.

Preferably said at least one organic liquid carrier is an oil (e.g. vegetable or mineral, or mixtures thereof).

Preferably said organic liquid phase includes a co-solvent.

Preferably said co-solvent is benzyl alcohol.

Preferably said aqueous phase includes a particulate content of either an active agent or an inert substance.

Preferably the particulate active agent is a biocide.

Optionally the composition includes in one or other, or both, of the partitioned phases one or more of the group comprising minerals and vitamins.

In another aspect the invention is **an anthelmintic composition** having

about 0.08% ivermectin,

about 3% levamisole, and

about 2% albendazole

where different liquid carrier phases substantially partition the ivermectin from the levamisole, and

where the albendazole is particulate and is at least in part in an aqueous phase with the levamisole, such aqueous phase being buffered to a pH appropriate for the levamisole and its stability.

All percentages are expressed as w/v except where otherwise stated.

In another aspect the present invention consists in **a storage stable pourable pesticidal composition** having an organic first liquid phase and another ("second") liquid phase, said first phase including at least one active ingredient (and optionally a co-solvent for said active ingredient) and said second phase including a second active ingredient

whereinthe presence of an emulsifying agent and/or anti-flocculants ensures stability of the two phases with the first phase with its first active ingredient as an emulsion within said second phase with its second active ingredient.

Preferably said second phase is an organic acid and/or aqueous phase.

Preferably said second phase comprises or includes an organic acid such as lactic acid.

Preferably said first phase comprises an oil and/or emollient ester.

Preferably said active ingredients in each of said phases or which might be present as an additional active in both or either phase comprises any of the examples hereinafter provided.

In another aspect the invention consists in **a stable mix of two or more immiscible liquids or liquid phases** held together by an emulsifier or emulsifiers where one phase is an organic water immiscible phase and another phase is an aqueous or organic phase (eg; water or organic acid(s) such as lactic acid).

In another aspect the present invention consists in **a benzimidazole composition** comprising an organic acid (such as lactic acid) and the benzimidazole dissolved therein.

In yet a further aspect the present invention consists in **a topical or pour-on benzimidazole composition** where the benzimidazole is solubilised in an organic acid (such as lactic acid).

In yet a further aspect the present invention consists in **a benzimidazole containing composition** where at least one phase is that of an organic acid (such as lactic acid) which solubilises at least one benzimidazole active ingredient.

In another aspect the invention consists in **a ready to use pesticidal veterinary liquid composition** of at least a first active in a first liquid phase and at least a second active in a second liquid phase, the phases forming a stable emulsion.

Optionally a third active may be present in one or other or both of said phases.

Optionally such third active may be suspended in at least one phase.

Preferably each of said first and second actives are dissolved (at least in part) in their respective phases.

In another aspect the present invention consists in **a preferably storage stable pourable composition** comprising or including

up to 25% w/v of at least one pesticide (hereafter "first active(s)") soluble in an organic phase,

1 to 60% w/v of an organic phase [such as a oil (vegetable or mineral) and/or emollient esters] (hereafter "first liquid phase") in which said first active(s) is (are) at least substantially soluble,

0 - 5% w/v of a cosolvent for said first active(s),

1 to 15% w/v of an emulsifying agent,

0 to 20% w/v of at least one further pesticidal active (hereafter "second active(s)") not substantially soluble in said first phase,

and,

means providing a second liquid phase,

said composition having at least most of said first active(s) in a first phase and said first phase being emulsified in the second phase which includes said second active(s).

In another aspect the present invention consists in **a preferably storage stable composition** (whether as a concentrate for aqueous dilution or otherwise) comprising or including

up to 25% w/v of at least one pesticide (hereafter "first active(s)") chosen from the class of at least partly oil or emollient ester soluble actives,

1 to 60% w/v of at least one water immiscible organic phase [such as a oil (vegetable or mineral) and/or emollient esters] in which said first active(s) is (are) at least substantially soluble,

0 - 5% w/v of a cosolvent for said first active(s),

1 to 15% w/v of an emulsifying agent,

0 to 20% w/v of at least one further pesticidal active (hereafter "second active(s)") not substantially soluble in said organic phase which is (i) dissolved in said water and/or (ii) suspended in said water,

and,

water,

said composition having an organic phase with at least most of said first active(s), said organic phase being emulsified in an aqueous phase of said water and said second active(s).

Preferably is one embodiment said first and second active are anthelmintics.

Preferably said organic phase at least includes an oil.

Preferably additional active ingredients are included in said composition whether in said organic phase or said aqueous phase or a mixture of them both.

In one preferred form of the present invention an additional active ingredient may be included in such a way that the composition is a suspo-emulsion.

In another aspect the present invention consists in **a storage stable pesticidal composition** having an organic phase and an aqueous phase, said organic phase being of an oil and/or emollient ester which includes at least one active ingredient (and optionally a co-solvent for said active ingredient) and an aqueous phase including a second active ingredient which is substantially insoluble in said organic phase **wherein** the presence of an emulsifying agent and/or anti-flocculants ensures stability of the two phases with the organic phase as an emulsion within said aqueous phase.

Preferably said composition includes still further actives which as particles, liposomes or as liquid globules are suspended in one or other or both of said phases. For instance preferably said first active may be a broad spectrum anthelmintic such as an ML anthelmintic (eg; abamectin) and said second active is a water soluble active also capable of killing nematodes such as levamisole. An additional active or additional actives may include one or more of suitable actives dissolvable or suspendible or emulsifiable in one or other of the phases having, for example, an additional anthelmintic, or an active with an ectoparasitocidal effect or a flukicidal effect.

Equally this may contain two or more actives that have activity against trematodes such as Flukes or Cestodes, or Ectoparasites.

In another aspect the present invention consists in **a pourable pesticidal composition** comprising or including

at least one active ingredient chosen from the class of macro cyclic lactones (hereafter "ML"),

at least one active ingredient chosen from the tetramisole/levamisole class,

at least one organic liquid carrier (preferably at least one oil and, optionally, at least one organic co-solvent) to provide a first liquid phase, and

means providing a second liquid phase,

and, optionally, an emulsifying agent or agents,

wherein said ML active ingredient(s) is(are) at least primarily in the first phase in solution,

and wherein said tetramisole/levamisole class active ingredient(s) is(are) at least primarily in solution in the second phase,

and wherein said phases exist in, or can be shaken or agitated into, the form of an emulsion.

In another aspect the present invention consists in **a pesticidal composition** (whether as a concentrate for aqueous dilution or otherwise) comprising or including

at least one active ingredient chosen from the class of macro cyclic lactones (hereafter "ML"),

at least one active ingredient chosen from the tetramisole/levamisole class,

at least one organic liquid carrier (preferably at least one oil and, optionally, at least one organic co-solvent), and

water,

and, optionally, an emulsifying agent or agents,

wherein said ML active ingredient(s) is(are) at least primarily in the organic liquid carrier(s) in solution (hereafter referred to as "the organic phase"),

and wherein said tetramisole/levamisole class active ingredient(s) is(are) at least primarily in solution in the water (hereafter referred to as "the aqueous phase"),

and wherein said organic phase and said aqueous phase exist in, or can be shaken into, the form of an emulsion.

Optionally a co-solvent is present. Preferably such co-solvent is selected from the class of alcohols having multiple carbons (preferably 4 or more) (eg; benzyl alcohol), diols and glycol ethers.

Preferably a third active ingredient is included in the composition.

In one form preferably said third ingredient (if an anthelmintic) is other than an ML anthelmintic and other than an anthelmintic chosen from the tetramisole/levamisole class.

Preferably said third anthelmintic agent is selected from the group including benzimidazoles and probenzimidazoles (eg; albendazole, oxfendazole, triclabendazole), praziquantel, salicylamides (eg; closantel), organophosphates, (napthalophos), clorsulon, nitroxynil, morantel, pyrantel, et al. - see Table 2 - Spectrum of Activity.

Preferably said third anthelmintic active ingredient is suspended at least primarily in the aqueous phase.

Preferably said aqueous phase includes at least one suspension agent for said third anthelmintic active ingredient.

In still other aspects the present invention consists in **a (preferably storage stable) pourable composition** comprising or including

at least one anthelmintic active (hereafter "first anthelmintic active(s)"),

at least one liquid to provide a first phase in which said first anthelmintic active(s) is (are) at least substantially soluble,

an emulsifying agent,

at least one liquid to provide a second phase, and

at least one further anthelmintic active (hereafter "second anthelmintic active(s)") not substantially soluble in said first phase,

said composition having a first phase with at least most of said first anthelmintic active(s) and a second phase of at least most of said second anthelmintic active(s).

In still other aspects the present invention consists in **a (preferably storage stable) composition** (whether as a concentrate for aqueous dilution or otherwise) comprising or including

at least one anthelmintic (hereafter "first anthelmintic active(s)") chosen from the class of at least partly oil soluble anthelmintic actives,

at least one oil (optionally also with an organic co-solvent) in which said first anthelmintic active(s) is (are) at least substantially soluble,

an emulsifying agent,

water, and

at least one further anthelmintic active (hereafter "second anthelmintic active(s)") not substantially soluble in said oil(s) which is (i) dissolved in said water and/or (ii) suspended in said water,

said composition having an organic phase of said oil(s) with at least most of said first anthelmintic active(s) and an aqueous phase of said water and at least most of said second anthelmintic active(s).

Preferably said oil is a vegetable oil or a mineral oil.

Preferably said composition includes a third active.

Preferably said third active is a therapeutic agent such as an antimicrobial and/or still further anthelmintic active (eg; flukicide) and/or an ectoparasitocide (hereinafter "third active(s)").

Preferably said third active(s) is primarily disposed within said aqueous phase although in other forms of the present invention it may be partitioned between the organic and aqueous phases or largely in the organic phase.

Preferably said second anthelmintic active(s) is dispersed substantially homogeneously as a suspension in the water.

Preferably said composition includes any one or more of the following:

- a co-solvent which is to form part of said aqueous phase, eg; as maybe preferable if the first anthelmintic active(s) is only partially soluble in the vegetable oil(s),
- mineral(s),
- vitamin(s),
- antimicrobial(s),
- anthelmintic(s),
- antifreeze(s),
- thickening agent(s),
- anti-focculant(s),
- pH stabiliser(s).

Preferably said vegetable oil(s) is selected from the group including soyabean oil, sesame seed oil, corn oil, sunflower oil, peanut oil and safflower oil.

Preferably said emulsifying agent is Tween 80 and/or Teric 380.

Preferably said second anthelmintic active is selected from the group consisting of levamisole or tetramisole (if a water phase soluble anthelmintic) or a water phase suspendible

or dispersible anthelmintic such as a suitable benzimidazole typified by, for example, albendazole or oxfendazole. Alternatively said optional third active is a dispersed benzimidazole.

Preferably said cosolvent is selected from the group including high chain alcohols (such as benzyl alcohol), diols, glycol ethers, and esters (eg; PMP).

Preferably said antimicrobial is selected from the group including benzoic acid, potassium sorbate and parabens.

Preferably said minerals are selected from the group including mineral salts or chelates, eg; selenium, copper, cobalt, iodine and zinc.

Preferably said vitamins are selected from the group including vitamins A, D, E, B and C.

Preferably said antifreeze or freezes is or are selected from the group consisting of propylene glycol and glycerine.

Preferably said thickening agent are selected from the group of cellulose gum, xanthan gum, carbapol and algeinates.

Preferably said anti-flocculants are selected from the group consisting of Terasperse 2500 and 4896 (preferably both).

Preferably said pH stabilisers are selected from the group consisting of citric acid, phosphate salts, etc.

Preferably the or a said organic liquid carrier is an oil.

Preferably said oil is a vegetable oil. In other forms it is a mineral oil (eg; medium grade).

Preferably said vegetable oil is selected from a group consisting of or including soyabean oil, corn oil, sesame seed oil, sunflower oil, peanut oil and safflower oil.

In yet a further aspect the present invention is **a stable formulation** of

a first active in an organic ("first") phase,

a second active in a second liquid phase, and

additional actives in one or other, or both, said phase(s),

and wherein said phases provide a stable emulsion,

and wherein at least one (and preferably both) of said first and second actives is (are) an anthelmintic active.

Preferably a third active is a suspended active at least primarily in the second phase (eg; an anthelmintic or ectoparasiticide).

Preferably an emulsifying agent assists in the stability of the emulsion.

In yet a further aspect the present invention is **a stable formulation** of

a first active in an organic phase at least primarily of oil(s),

a second active in an aqueous phase, and

additional actives in one or other, or both, said organic and aqueous phase(s),

and wherein said organic and aqueous phases provide a stable emulsion,

and wherein at least one (and preferably both) of said first and second actives is (are) an anthelmintic active.

Preferably a third active is a suspended active at least primarily in the aqueous phase (eg; an anthelmintic or ectoparasiticide).

Preferably an emulsifying agent assists in the stability of the emulsion.

In another aspect the invention consists in **a storage stable and pourable pesticidal composition** comprising or including

(i) at least one active ingredient chosen from the class of macro cyclic lactones (hereafter "ML"),

(ii) at least one organic liquid carrier which carries at least most of said ML active ingredient(s), thereby defining an organic liquid phase,

(iii) levamisole, and

(iv) at least water which carries at least most of said levamisole thereby defining an aqueous phase,

wherein said aqueous phase has a pH of less than 7,

and wherein there is present in said aqueous phase either or both

(a) an emulsifying agent or agents, and

(b) a particulate content,

and wherein said phases exist in, or can be shaken or agitated into, the form of an emulsion with said particulate content, if any, at least substantially present in the aqueous phase.

In yet another aspect the invention is **an anthelmintic oil in water emulsion** carrying at least one macro cyclic lactone (ML) in the oil phase and particles of levamisole and an emulsifying agent for the levamisole in the aqueous phase.

In still another aspect the invention is **a partitioned biocidal composition** comprising in an organic phase a first biocide, and in an aqueous phase at acid pH a second biocide, said first biocide being unstable chemically at said acid pH.

Preferably said composition has particles suspended in at least the aqueous phase.

Preferably said particles are themselves biocidal.

Preferably said particles are of a benzimidazole anthelmintic.

In a further aspect the invention consists in **a method of formulating an anthelmintic composition** of a kind having

at least one anthelmintic (hereafter "first active(s)"),

a liquid or liquids to define a first phase in which said first active(s) is (are) at least substantially soluble,

(optionally) an emulsifying agent,

at least one further anthelmintic active (hereafter "second active(s)") not substantially soluble in said first phase

(optionally) anti-flocculant(s),

and,

a liquid or liquids to define a second phase,

said method comprising or including the steps of

(I)(a) providing a mix of said first active ingredient and at least the first phase liquid(s),

(b) providing a mix of said second active ingredient and at least the second phase liquid(s), and

(II) by mixing at least the mixes of (I)(a) and (I)(b) forming an emulsion with at least most of said first active in the first phase and at least most of the second active in the second phase.

In a further aspect the invention consists in **a method of formulating an anthelmintic composition** of a kind having

at least one anthelmintic (hereafter "first active(s)") chosen from the class of (at least partly) oil soluble anthelmintic actives,

an oil or oils in which said first active(s) is (are) at least substantially soluble,

optionally a cosolvent for said first active(s),

an emulsifying agent,

at least one further anthelmintic active (hereafter "second active(s)") not substantially soluble in said oil(s),

optional anti-flocculant(s),

and,

water,

said method comprising or including the steps of

(I)(a) providing a mix of said first active ingredient, the oil(s), the optional co-solvent(s) and the emulsifying agent(s),

(b) providing a mix of said second active ingredient the water, and the optional anti-flocculant(s), and

(II) by mixing at least the mixes of (I)(a) and (I)(b) forming an emulsion with at least most of said first active in the oil(s) and at least most of the second active in the aqueous phase.

In yet a further aspect the invention consists in **an anthelmintic composition** so made.

In still other aspects the invention is **a method of treating mammals for pests** which involves (whether with dilution or not) administering or having self administered to such mammals effective amounts of active(s) of compositions of the present invention.

In still a further aspect the invention consists in **the use of an anthelmintic composition** of any of the kinds previously defined.

In some forms said use is as an oral, a pour-on or as a parenteral composition (preferably with an anthelminticly effective amount of each active).

Preferred formulations of the present invention comprise:

Component 1 - water insoluble but mostly or completely oil soluble anthelmintic active.

Component 2 - An oil (vegetable or mineral)

Component 3 - an emulsifying agent

Component 4 - water

Component 5A, 5B, etc. - Additional active(s) of which at least one is preferably an anthelmintic active. This or these can be either dissolved in the water phase (such as Levamisole) or suspended in the water phase (such as Albendazole) if insoluble, or both (eg; Levamisole and Albendazole).

The water insoluble active is dissolved in the oil, which is emulsified in water. The oil protects the active against the pH or constituents present in the water phase.

Additional components can be added to this basic formulation.

Addition 1 - if component 1 is only partially soluble in the oil phase then a co-solvent may be necessary (eg; an organic co-solvent).

Addition 2 - Minerals/Vitamins

Addition 3 - An antimicrobial.

Addition 4 - Antifreezes.

Addition 5 - Thickening agents.

Addition 6 - Anti-flocculants.

Addition 7 - pH stabilisers.

Preferred components and their concentration ranges and examples are set out in **Table 1:**

Table 1	Function	Examples	% W/V
Component 1	Active	Abamectin or ivermectin	0 - 25%
Component 2	Vegetable Oil Mineral Oil	Soya bean Medium Grade	1 - 60% 1 - 60%
Component 3	Emulsifying Agent	Tween 80 Teric 380	1 - 15%
Component 4	Water		To Volume
Component 5A, 5B, etc.	Additional anthelmintic Water soluble Water Insoluble	 Levamisole Albendazole or oxfendazole	 0 - 15% 0 - 20%
Addition 1	Co-Solvent	Includes high chain Alcohols (such as Benzyl Alcohol), diols such as PMP (promyristyl propionate), Glycol Ethers and Esters	0 - 5%
Addition 2	Minerals	Mineral salts or chelates	0 - 5%
Addition 3	Antimicrobials	Benzoic Acid, Potassium Sorbate and Parabens, Benzyl Alcohol	0 - 1%
Addition 4	Antifreeze	Propylene Glycol, Glycerine	0 - 5%
Addition 5	Thickening Agents	Cellulose Gum, Xanthan Gum, Carbapol and Algeinates	0 - 3%
Addition 6	Anti-flocculants	Terasperse 2500 and 4896	0 - 7%
Addition 7	pH Stabilisers	Citric Acid, Phosphate salts etc.	0 -05%

Preferred actives by reference to activity are now tabulated.

Table 2 - Spectrum of Activity

Compound	Nematodes		Cestodes	Trematodes	Protozoa	Ectoparasites			
	Gastrointestinal Worms	Lung-worms	Tapeworms	Fluke		Lice	Mites	Ticks	Flies

Compound	Nematodes		Cestodes	Trematodes	Protozoa	Ectoparasites			
A. Macrocyclic Lactones									
1. Avermectins									
Ivermectin	+	+	-	_		+	+	+	+
Abamectin	+	+	-	-		+	+	+	+
Doramectin	+	+	_	_		+	+	+	+
Eprinomectin	+	+				+	+	+	+
2. Milbemycin									
Moxidectin	+	+	-	-		+	+	+	+
B. Benzimidazoles									
1. Probenzimidazoles									
Febantel	+	+							
Netobimin	+	+							
2. Benzimidazoles (thiazoles)									
Thiabendazole	+	+							
Cambendazole	+	+							
3. Benzimidazoles (carbamates)									
Albendazole	+	+	+	+	+(Giardia)	-	-	-	-
Fendendazole	+	+		+	+(Giardia)	-	-	-	-
Mebendazole	+	+				-	-	-	-
Rycobendazole	+	+	+	+		-	-		
Oxfendazole	+	+	+	+		-	-		
Parrbendazole	+	+		-					
Triclabendazole	-	-	-	+		-	-		-
C. Imidazothiazole									
Levamisole	+	+							
D. Tetrahydropyrimidazole									
Morantel	+		+						
Pyrantel	+								
E. Salicylamidides									
Closantel	+(Haemonchus)	-	-	+					+

Compound	Nematodes		Cestodes	Trematodes	Protozoa	Ectoparasites			
Oxyclosanide	+(Haemonchus)			+					
Rafoxamide	+(Haemonchus)								
Niclosamide			+						
F. Benzoenedisulphonamide									
Clorsulon	-	-	-	+					
G. Nitrophenolic Compounds									
Nitroxyinil	+(Haemonchus)	-	-	+					+
H. Pyrazinoisoquinoline									
Praziquantel	-	-	+						
I. Organophosphates									
Napthalophos	+								
Trichlorphon	+								+
Propetamphos									+
Diazinon						+	+		+
Cumaphos						+	+	+	+
J. Synthetic Pyrethroids									
Cypermethrin						+			+
Alphamethrin						+			+
Flumethrin								+	
K. Insect Growth Regulators									
Diflubenzuron						+			+
Triflumuron						+			
Cyromazine									+
L. Amitraz								+	

Compound	Nematodes		Cestodes	Trematodes	Protozoa	Ectoparasites			
M. Cyhalothrin								+	+
N. GABA Inhibitor									
Fipronil						+	+	+	+

Preferred forms of the present invention will hereafter be described by reference to examples and the accompanying drawings in which

Figure 1 is a plot from the cattle trial NCOO1 hereafter referred to of Avermectin B1a blood levels (ng/mL) against time (hours) for the different modes of administration,

Figure 2 is a plot of Levamisole blood levels (μg/ml) against time (hours) for the different modes of administration in cattle,

Figure 3 is a plot of Oxfendazole blood levels (μg/ml) against time (hours) for the different modes of administration in cattle,

Figure 4 is a plot of Fenbendazole blood levels (μg/ml) against time (hours) for the different modes of administration in cattle,

Figure 5 is a plot of Avermectin B1a blood level (ng/mL) against time (hours) for the oral combination against a commercial oral formulation in sheep,

Figure 6 is a plot of Levamisole blood level (μg/ml) against time (hours) for the oral combination against a commercial oral formulation in sheep,

Figure 7 is a plot of Albendazole blood levels (μg/ml) against time (hours) for the oral combination against a commercial oral formulation in sheep,

Figures 8 to 10 are stability graphs for each of Abamectin, Levamisole and Albendazole against Time respectively for formulation LB98/92,

Figure 11 is a plot of Levamisole content against Time for formulation LB98/92,

Figure 12 is a plot of pH against Time for formulation LB98/92,

Figure 13 shows stability results and graphs for formulation LB99/01 of Table 7,

Figure 14 shows stability results and graphs for formulation LB99/02 of Table 8,

Figure 15 shows stability results and graphs for formulation LB99/03 of Table 9,

Figure 16 stability graphs of pH changes with time for formulations LB99/54A, LB99/54B, LB99/54C and LB99/54D of Table 10,

Figure 17 shows (for a 50°C accelerated stability trial) the change of pH of formulations/drenches of Tables 12 and 13 with time,

Figure 18 shows (for a 50°C accelerated stability trial) the change of viscosity (cp) of formulations/drenches of Tables 12 and 13 with time,

Figure 19 shows (for a 50°C accelerated stability trial) the change of mean droplet/particle size of formulations/drenches of Tables 12 and 13 with time.

Figure 20 shows (for a 50°C accelerated stability trial) the change of moisture content of formulations/drenches of Tables 12 and 13 with time,

Figure 21 shows (for a 50°C accelerated stability trial) the change of levamisole content of formulations/drenches of Tables 12 and 13 with time,

Figure 22 shows (for a 50°C accelerated stability trial) the change of praziquantel content of formulations/drenches of Tables 12 and 13 with time,

Figure 23 shows (for a 50°C accelerated stability trial) the change of albendazole content of formulations/drenches of Tables 12 and 13 with time,

Figure 24 shows (for a 50°C accelerated stability trial) the change of ivermectin content of formulations/drenches of Tables 12 and 13 with time,

Figure 25 shows (for a 50°C accelerated stability trial) the change of abamectin content of formulation/drenches of Tables 12 and 13 with time,

Figure 26 shows (for a 50°C accelerated stability trial) the change of benzyl alcohol content of formulations/drenches of Tables 12 and 13 with time,

Figure 27 shows (for a 50°C accelerated stability trial) the change of selenium content of formulations/drenches of Tables 12 and 13 with time,

Figure 28 shows (for a 50°C accelerated stability trial) the change of cobalt content of formulations/drenches of Tables 12 and 13 with time,

Figure 29 shows the positive effect against clumping/aggregation from the presence of particles of Levamisole hydrochloride, the unclumped dish to the right being that (LB99/96C of Table 14) with Levamisole, the others (LB99/96A and LB99/96B of Table 14) having no such presence and clumping,

Figure 30 shows the results of freeze/thaw trials (mLs separation - 200mL samples being cycled between minus 4°C and ambient for 4 days) for formulations/drenches of Table 15, and

Figure 31 shows a photograph of phase separation(A) after freeze thawing compared with a stable homogeneous formulation(B) of the invention.

In the following examples all percentages are weight to volume. These examples show various formulations directed to a resistance strategy which nevertheless are stable and may have additional therapeutic and/or active inclusions.

EXAMPLE 1

Combination Abamectin/Levamisole Drench

Abamectin	0.20 % w/v
Tween 80	8.00 % w/v
Benzyl Alcohol	3.00 % w/v
Propylene Glycol	20.00 % w/v
Na_2HPO_4	1.03 % w/v
Citric Acid	0.29 % w/v
Levamisole HCL	8.00 % w/v
Sodium Selenate	0.24 % w/v
Water	To Volume % w/v

This was formulated as follows at ambient temperature.

- Mix 1 - Dissolved Abamectin in Benzyl Alcohol, mixed in Tween and Propylene Glycol.
- Mix 2 - Dissolved Levamisole, Na_2HPO_4, Citric acid and Sodium Selenate in water.
- Combined mix 1 and 2.

This resultant formulation was physically stable but considered too thin.

To correct this the following Examples 2 - 4 were thickened with Carbopol or gums.

EXAMPLE 2

Combination Abamectin/Levamisole Drench

Abamectin	0.20 % w/v
Tween 80	8.00 % w/v
Benzyl Alcohol	3.00 % w/v
Propylene Glycol	20.00 % w/v

Na_2HPO_4	1.03 % w/v
Citric Acid	0.29 % w/v
Levamisole HCL	8.00 % w/v
Sodium Selenate	0.24 % w/v
Cellulose Gum CMC	0.50 % w/v
Water	To Volume % w/v

This was formulated as follows;

- Mix 1 - Dissolved Abamectin in Benzyl Alcohol then add Tween.
- Mix 2 - Dissolved Levamisole, Na_2HPO_4, Citric acid and Sodium Selenate in water.
- Mix 3 - Dispersed thickener in Propylene glycol.
- Combined Mix 2 and 3 then added Mix 1.

EXAMPLE 3

Combination Abamectin/Levamisole Drench

Abamectin	0.20 % w/v
Tween 80	8.00 % w/v
Benzyl Alcohol	3.00 % w/v
Propylene Glycol	20.00 % w/v
Na_2HPO_4	1.03 % w/v
Citric Acid	0.29 % w/v
Levamisole HCL	8.00 % w/v
Sodium Selenate	0.24 % w/v
Carbopol 934	0.50 % w/v
Water	To Volume % w/v

EXAMPLE 4

Combination Abamectin/Levamisole Drench

Abamectin	0.20 % w/v
Tween 80	8.00 % w/v
Benzyl Alcohol	3.00 % w/v
Propylene Glycol	20.00 % w/v
Na_2HPO_4	1.03 % w/v
Citric Acid	0.29 % w/v
Levamisole HCL	8.00 % w/v
Sodium Selenate	0.24 % w/v
Xanthan Gum	0.20% w/v
Water	To Volume % w/v

The low pH of these formulations 2, 3 and 4 (pH<4) was identified as unsuitable for long the long-term stability of Abamectin. These completely aqueous formulation approaches were then stopped and it was decided to use a vegetable oil to attempt to encapsulate the Abamectin and possibly protect if from the low pH of the water phase. An additional active, albendazole, a benzimidazole anthelmintic, was added to the formulation.

EXAMPLE 5

Combination Abamectin/Albendazole/Levamisole Drench

Abamectin	0.10 % w/v
Albendazole	2.50 % w/v
Benzyl Alcohol	3.00 % w/v
Teric 215	10.0 % w/v
Teric 216	10.0 % w/v
Propylene Glycol	3.00 % w/v
Na_2HPO_4	1.05 % w/v
Citric Acid	1.21 % w/v
Levamisole HCL	3.75 % w/v
Sodium Selenate	0.12 % w/v
Cobalt EDTA	0.36 % w/v
Soyabean Oil	3.00 % w/v
Xanthan gum	0.32 % w/v
Water	To Volume % w/v

This was formulated as follows:

- Mix 1 - Dissolve Abamectin in Benzyl Alcohol. Mix in Terics.
- Mix 2 - Dissolve Levamisole, Cobalt-ETDA, Citric acid, Na_2HPO_4 and Sodium Selenate in water.
- Mix 3 - Disperse Xanthan gum in Propylene glycol then add 5% of water to form gel.
- Combine Mix 1 and 2. Added Albendazole. Then added Mix 1.

This formulation after 2 months accelerated stability assays shows that the Abamectin was degrading. The physical stability of this formulation was also poor with Albendazole flocculating out and with the oil phase showing evidence of curdling.

EXAMPLE 6

Combination Abamectin/Albendazole/Levamisole Drench

Abamectin	0.10 % w/v
Albendazole	1.90% w/v
Benzyl Alcohol	3.00 % w/v
Teric 215	10.0 % w/v
Teric 216	10.0 % w/v
Propylene Glycol	3.00 % w/v
Na_2HPO_4	1.05 % w/v
Citric Acid	1.21 % w/v
Levamisole HCL	3.75 % w/v
Sodium Selenate	0.12 % w/v
Cobalt EDTA	0.36 % w/v
Soyabean Oil	3.00 % w/v
Xanthan gum	0.32 % w/v
Water	To Volume % w/v

This formulation like that of Example 6 after 2 month accelerated stability assays also showed that Abamectin was degrading. The physical stability of this formulation was also poor with Albendazole flocculating out and with the oil phase showing evidence of curdling.

To prevent such flocculation Terasperse 4896 and Terasperse 2500 were then trialed. These theoretically coat the Albendazole and *improve the solubility in water.*

Teric 380, a more appropriate emulsifying agent for stable vegetable oil emulsions.

The percentage of the oil phase was increased to 10% to increase the partition between the oil/water phase possibly improve Abamectin stability.

EXAMPLE 7

Combination Abamectin/Albendazole/Levamisole Drench

Abamectin	0.10 % w/v
Albendazole	1.90 % w/v
Benzyl Alcohol	3.00 % w/v
Terasperse 4896	1.00 % w/v
Terasperse 2500	2.00 % w/v
Teric 380	5.00 % w/v
Propylene Glycol	3.00 % w/v
Levamisole HCl	4.00 % w/v
Sodium Selenate	0.12 % w/v
Cobalt EDTA	1.50 % w/v

Soyabean Oil	10.00 % w/v
Xanthan gum	0.20 % w/v
Water	To Volume % w/v

This was formulated as follows:

- Mix 1 - Dissolved Abamectin in Benzyl Alcohol. Mix into soyabean oil. Mix in Teric 380.
- Mix 2 - Added Albendazole and Terasperses to water. Added Levamisole, Cobalt-ETDA. Citric acid and Sodium Selenate.
- Mix 3 - Dispersed Xanthan gum in Propylene glycol then added 5% of water to form gel.
- Combined Mix 1, 2 and 3.

This formulation gave no flocculation but the oil phase readily separated out.

The oil/water phase required further stabilisation. A series of water/oil/emulsifier blends were prepared to optimise this aspect of the formulation. Tween 80 was also trialed as a possible alternative emulsifier to Teric 380. All formulations were stored at ambient.

EXAMPLE 8

Oil/Water Blends

Tween 80	10.0 % w/v
Soyabean Oil	10.0 % w/v
Water	To Volume % w/v

This was prepared as a simple mixture but the emulsion broke after 4 hours.

EXAMPLE 9

Oil/Water Blends

Teric 380	5.0 % w/v
Soyabean Oil	10.0 % w/v
Water	85.0 % w/v

This straight blend broke after 2 days.

EXAMPLE 10

Oil/Water Blends

Tween 80	10.0 % w/v
Soyabean Oil	50.0 % w/v
Water	40.0 % w/v

This straight blend emulsion broke after 4 days.

EXAMPLE 11

Oil/Water Blends

Teric 380	5.0 % w/v
Soyabean Oil	50.0 % w/v
Water	45.0 % w/v

This straight blend emulsion broke after 25 days.

As a result we concluded that

- Teric 380 was the better emulsifier, and
- the higher concentration of oil emulsion was the most stable option. Therefore we decided to trial with oil at from 35 to 60% w/v.

EXAMPLE 12

40% Soyabean Oil

Abamectin	0.10 % w/v
Albendazole	1.90 % w/v
Benzyl Alcohol	3.00 % w/v
Terasperse 4896	1.00 % w/v
Terasperse 2500	2.00 % w/v
Teric 380	5.00 % w/v
Propylene Glycol	3.00 % w/v
Levamisole HCl	4.00 % w/v
Sodium Selenate	0.12 % w/v
Cobalt EDTA	1.50 % w/v
Soyabean Oil	40.00 % w/v
Xanthan gum	0.30 % w/v
Water	To Volume % w/v

This was formulated as follows at ambient temperature.

- Mix 1 - Dissolved Abamectin in Benzyl Alcohol. Mix into Soyabean oil. Mix in Teric 380.
- Mix 2 - Added albendazole and Terasperses to water. Added levamisole, Cobalt-ETDA, Citric acid and Sodium Selenate.
- Mix 3 - Dispersed Xanthan gum in Propylene glycol then added 5% of water to form gel. Combined Mix 1, 2 and 3.

With this formulation we found no flocculation occurred or separation of the oil was observed. This batch has remained stable after being recycling between 4°C, ambient and 30°C for 6 months.

Although formulation of Example 12 was showing indications of suitability another formulation option was tested. Xanthan Gum was replaced with Alginate as a alternative thickener.

EXAMPLE 13

Combination Abamectin/Albendazole/Levamisole Drench with alginates

Abamectin	0.10 % w/v
Albendazole	1.90 % w/v
Benzyl Alcohol	3.00 % w/v
Terasperse 4896	1.00 % w/v
Terasperse 2500	2.00 % w/v
Teric 380	5.00 % w/v
Propylene Glycol	3.00 % w/v
Levamisole HCL	4.00 % w/v
Sodium Selenate	0.12 % w/v
Cobalt EDTA	1.50 % w/v
Soyabean Oil	10.00 % w/v
Alginate (Kelcolid)	0.20 % w/v
Water	To Volume % w/v

Formulating Order:

- Mix 1 - Dissolved Abamectin in Benzyl Alcohol. Mix into soyabean oil. Mix in Teric 380.
- Mix 2 - Added Albendazole and Terasperses to water. Added Levamisole, Cobalt-ETDA, Citric acid and Sodium Selenate.

- Mix 3 - Dispersed Alginate in Propylene glycol then added 5% of water to form gel.
- Combined Mix 1, 2 and 3.

Findings:

- Product appeared stable but a rapid viscosity drop with time was observed. This was followed by eventual slight separation of the water phase in long term stability samples.

EXAMPLE 14 (Batch No. LB99/01)

Increasing Benzimidazole (Albendazole) Loading

Abamectin	0.10 % w/v
Albendazole	**2.38 % w/v**
Benzyl Alcohol	3.00 % w/v
Terasperse 4896	1.00 % w/v
Terasperse 2500	2.00 % w/v
Teric 380	5.00 % w/v
Propylene Glycol	3.00 % w/v
Levamisole HCL	3.75 % w/v
Soyabean Oil	40.00 % w/v
Xanthan gum	0.30 % w/v
Water	To Volume % w/v

Formulating Order:

- Mix 1 - Dissolved Abamectin in Benzyl Alcohol. Mix into soyabean oil. Mix in Teric 380.
- Mix 2 - Added Albendazole and Terasperses to water. Added Levamisole and Citric Acid.
- Mix 3 - Dispersed Xanthan gum in Propylene glycol then added 5% of water to form gel.
- Combined Mix 1, 2 and 3.

Findings:

- Product stable under an accelerated stability programme.

The robustness of this formulation concept was examined by substituting Albendazole with Oxfendazole and by increasing active loading.

EXAMPLE 15 (Batch No. LB99/03)

Substituting Albendazole with Oxfendazole

Abamectin	0.10 % w/v
Oxfendazole	2.26 % w/v
Benzyl Alcohol	3.00 % w/v
Terasperse 4896	1.00 % w/v
Terasperse 2500	2.00 % w/v
Teric 380	5.00 % w/v
Propylene Glycol	3.00 % w/v
Levamisole HCL	3.75 % w/v
Soyabean Oil	40.00 % w/v
Xanthan gum	0.30 % w/v
Water	To Volume % w/v

Formulated similarly to Example 14.

Findings:

- Product stable under an accelerated stability programme.

EXAMPLE 16

Increasing Albendazole Loading

Abamectin	0.10 % w/v
Albendazole	5.00 % w/v
Benzyl Alcohol	3.00 % w/v
Terasperse 4896	2.00 % w/v
Terasperse 2500	4.00 % w/v
Teric 380	5.00 % w/v
Propylene Glycol	3.00 % w/v
Levamisole HCL	3.75 % w/v
Soyabean Oil	35.00 % w/v
Xanthan gum	0.30 % w/v
Water	To Volume % w/v

Prepared similarly to Example 14.

Findings:

- Product stable under an accelerated stability programme.

EXAMPLE 17

Benzimidazole Active in Lactic Acid

Carnola Oil	40.00 % w/v
Teric 380	5.00 % w/v
Abamectin	0.10% w/v
Promyristyl Propionate	3.00 % w/v
Oxfendazole	4.00 % w/v
Levamisole HC1	3.75% w/v
Lactic Acid	To volume

Formulated Order:

- Mix 1 - Dissolve Abamectin in warmed emollient Ester (Promyristyl Propionate) then mix into Oil. Mix in Teric 380.
- Mix 2 - To Lactic acid dissolve Oxfendazole and Levamisole (slight heat required).
- Mix 3 - Combine mixes 1 and 2 with high shear agitation

Findings:

- These soluble forms of benzimidazoles are likely to have advantage (more easily dermally absorbed) as pour-on formulations. May include a thickener.

EXAMPLE 18

Benzimidazole Active in Lactic Acid

Carnola Oil	40.00 % w/v
Teric 380	5.00 % w/v
Abamectin	0.10% w/v
Promyristyl Propionate	3.00 % w/v
Triclabendazole	0.50% w/v
Oxfendazole	4.00% w/v
Levamisole HC1	3.75% w/v
Lactic Acid	To Volume

Formulated Order:

- Mix 1 - Dissolve Abamectin in warmed emollient Ester (Promyristyl Propionate) then mix into Oil. Mix in Teric 380.

- Mix 2 - To Lactic acid dissolve Oxfendazole or Levamisole and Triclabendazole (slight heat required).
- Mix 3 - Combine mixes 1 and 2 with high shear agitation

Findings:

- As above, likely to have application as a pour-on formulation. May include a thickener.

STABILITY

Stability testing with formulations such as Example 7 over 19 months shows a desirability for buffering and a buffering system (citric acid/NaOH) was added. Laboratory Batch abbreviated to LB and is used synonymously with Batch Number (B/N).

Table 3

- LB98/92 - Abamectin 0.10%, Albendazole 1.9% and Levamisole 4.0% Triple Active Drench. Stability Conditions 4°C, Ambient and 30°C.

Formulation

Material	LB98/92
Soybean Oil	40.00% w/v
Ethoxylated Caster Oil	5.00% w/v
Abamectin @90%	0.11% w/v
Benzyl Alcohol	3.00% w/v
Albendazole @ 100%	1.90% w/v
Terasperse 4896	1.00% w/v
Terasperse 2500	2.00% w/v
Cobalt - EDTA	1.57% w/v
Sodium Selenate	0.12% w/v
Levamisole HCl @ 100%	4.00% w/v
Propylene Glycol	3.00% w/v
Xanthan Gum	0.30% w/v
Citric Acid	0.10% w/v
Water to volume	As required (to 100%)

Summary:

See Table 4 (4A, 4B and 4C) for stability results at 4°C, Ambient and 30°C.

See Figures 8 to 10 for stability graphs for Abamectin, Levamisole and Albendazole respectively.

See Figures 11 and 12 for graphs with a comparison of pH (Figure 12) and Levamisole content (Figure 11).

Chemical stability appears satisfactory up until 13 month whereafter the pH drifts upwards and Levamisole contents drops. This pH drift/levamisole drop is believed related. Hence pH stabilisation is believed desirable.

TABLE 4

Sample ID: LB98-92

Storage conditions: 4°C, Ambient and 30°C.

Table 4A Stability Summary. 4°C, Ambient Humidity

Criteria	Initial Results	Age/Months at 4°C						
		1	2	3	6	9	13	19
Appearance	Homogeneous pink suspension.	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms
Specific Gravity	0.9970 @ 20°C	0.9970	0.9970	0.9970	0.9970	0.9970	0.9970	0.9970
Ph	3.85	3.85	3.95	3.85	3.85	3.80	4.00	4.35
Viscosity (Spindle 2 @ 12rpm)	483cps @ 20°C	413cps	406cps	386cps	366cps	352cps	374cps	334cps
Abamectin (aim 0.10%)	0.100%w/v	0.099%	0.100%	0.100%	0.098%	0.103%	0.097%	0.094%
Albendazole (aim 1.9%)	1.88%w/v	1.86%	1.77%	1.84%	1.90%	1.92%	1.90%	1.92%
Levamisole (aim 4.0%)	4.13%w/v	4.13%	4.09%	4.08%	4.03%	3.94%	3.98%	3.81%

Table 4B - LB 98/92 Stability Summary. Ambient Temperature and Humidity

Criteria	Initial Results	Age/Months at Ambient						
		1	2	3	6	9	13	19
Appearance	Homogeneous pink suspension.	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms
Specific Gravity	0.9970 @ 20°C	0.9970	0.9970	0.9970	0.9970	0.9970	0.9970	0.9970
Ph	3.85	3.85	3.90	3.95	3.95	3.90	3.80	4.45
Viscosity (Spindle 2 @ 12rpm)	483cps @ 20°C	330cps	307cps	284cps	276cps	252cps	267cps	334cps
Abamectin (aim 0.10%)	0.100%w/v	0.101%	0.101%	0.101%	0.101%	0.103%	0.099%	0.093%
Albendazole (aim 1.9%)	1.88%w/v	1.88%	1.86%	1.90%	1.87%	1.89%	1.90%	1.93%
Levamisole (aim 4.0%)	4.13%w/v	4.13%	4.14%	4.09%	4.03%	4.16%	3.92%	3.48%

Table 4C LB98/92 Stability Summary. 30°C and Ambient Humidity:

Criteria	Initial Results	Age/Months at 30°C						
		1	2	3	6	9	13	19
Appearance	Homogeneous pink suspension.	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms
Specific Gravity	0.9970 @ 20°C	0.9970	0.9970	0.9970	0.9970	0.9970	0.9970	0.9970
Ph	3.85	3.83	3.90	3.90	3.85	3.70	3.80	4.65
Viscosity (Spindle 2 @ 12rpm)	483cps @ 20°C	278cps	254cps	245cps	261cps	301cps	311cps	316cps
Abamectin (aim 0.10%)	0.100%w/v	0.100%	0.101%	0.101%	0.102%	0.100%	0.100%	0.092%
Albendazole (aim 1.9%)	1.88%w/v	1.89%	1.65%	1.83%	1.87%	1.84%	1.90%	1.93%
Levamisole (aim 4.0%)	4.13%w/v	4.08%	3.97%	4.09%	4.03%	4.10%	3.95%	3.54%

VARIATION IN BENZIMIDAZOLE CONTENT

Formulations

Table 5

LB 99/01	Abamectin 0.10%	Albendazole 2.38%	Levamisole 3.75%
LB 99/02	Abamectin 0.10%	Albendazole 5.00%	Levamisole 3.75%
LB 99/03	Abamectin 0.10%	Oxfendazole 2.26%	Levamisole 3.75%

Stability Conditions - Ambient and 30°C for Formulations of Table 5.

Table 6

Material	LB 99/01	LB 99/02	LB 99/03
Soybean Oil	40.00%	35.00%	40.00%
Ethoxylated Caster Oil	5.00%	5.00%	5.00%
Abamectin @ 90%	0.11%	0.11%	0.11%
Benzyl Alcohol	3.00%	3.00%	3.00%
Albendazole	2.38%	5.00%	--
Terasperse 4896	1.00%	2.00%	1.00%
Terasperse 2500	2.00%	4.00%	2.00%
Oxfendazole @ 100%	--	--	2.26%
Levamisole HCl @ 100%	3.75%	3.75%	3.75%
Propylene Glycol	3.00%	3.00%	3.00%
Xanthan Gum	0.30%	0.30%	0.30%
Citric Acid	0.10%	0.10%	0.10%
Water to volume	As Required	As Required	As Required

- See Figure 13 and Table 7 for stability results and graphs for LB 99/01.
- See Figure 14 and Table 8 for stability results and graphs for LB 99/02.
- See Figure 15 and Table 9 for stability results and graphs for LB 99/03.

Table 7

LB99/01 Stability Summary. Sheep Drench containing Abamectin, Albendazole and Levamisole. Ambient and 30°C Temperature. Ambient Humidity

Product	LB99/01								
Age	Initial	T=1mth	T=1mth	T=6mths	T=6mths	T=9mths	T=9mths	T=15mths	15mths
Storage Conditions		@Ambient	@30°C	@Ambient	@30°C	@Ambient	@30°C	@Ambient	@30°C
Appearance	Homogeneous White Emulsion	Homogeneous White Emulsion	Homogeneous White Emulsion	Homogeneous White Emulsion	Homogeneous White Emulsion	Homogeneous White Emulsion	Homogeneous White Emulsion	Homogeneous White Emulsion	Homogeneous White Emulsion
Specific Gravity	0.973 @ 20°C	0.973 @ 20°C	0.973 @ 20°C	0.973 @ 20°C	0.973 @ 20°C	0.973 @ 20°C	0.973 @ 20°C	0.973 @ 20°C	0.973 @ 20°C
pH	3.70	3.60	3.65	3.30	3.30	3.18	3.00	3.09	2.96
Viscosity	2,410cps	2,278cps	2,265	2,340cps	2,202cps	2,240cps	2,192cps	2,221cps	2,206cps
Abamectin	0.097%	0.098%	0.099%	0.096%	0.095%	0.099%	0.097%	0.095%	0.094%
Albendazole	2.35%	2.33%	2.34%	2.30%	2.29%	2.26%	2.20%	2.17%	2.26%
Levamisole	3.76%	3.74%	3.77%	3.83%	3.77%	3.74%	3.70%	3.73%	3.74%

Table 8

LB99/02 Stability Summary. Cattle Drench containing Abamectin, Albendazole and Levamisole. Ambient and 30°C Temperature. Ambient Humidity

Product	LB99/02

Age	Initial	T=1mth	T=1mth	T=6mths	T=6mths	T=9mths	T=9mths	T=15mths	15mths
Storage Conditions		@Ambient	@30°C	@Ambient	@30°C	@Ambient	@30°C	@Ambient	@30°C
Appearance	Homogeneous White Emulsion	Homogeneous White Emulsion	Homogeneous White Emulsion	Homogeneous White Emulsion	Homogeneous White Emulsion	Homogeneous White Emulsion	Homogeneous White Emulsion	Homogeneous White Emulsion	Homogeneous White Emulsion
Specific Gravity	0.983	0.983	0.983	0.983	0.983	0.983	0.983	0.983	0.983
pH	3.5	3.45	3.40	3.20	3.30	3.00	3.00	3.00	2.95
Viscosity	2,390cps	2,213cps	2,199cps	2,100cps	1,880cps	2,080cps	1,910cps	2,010cps	1,870cps
Abamectin	0.096%	0.097%	0.101%	0.103%	0.096%	0.096%	0.098%	0.095%	0.092%
Albendazole	4.99%	4.97%	4.96%	4.97%	4.91%	4.87%	4.91%	4.82%	4.78%
Levamisole	3.78%	3.77%	3.74%	3.71%	3.72%	3.75%	3.69%	3.78%	3.56%

Table 9

LB99/03 Stability Summary. Drench containing Abamectin, Oxfendazole and Levamisole. Ambient and 30°C temperature.

Ambient Humidity

Product	LB99/03								
Age	Initial	T=1mth	T=1mth	T=6mths	T=6mths	T=9mths	T=9mths	T=15mths	15mths
		@Ambient		@Ambient	@30°C	@Ambient		@Ambient	
Appearance	Homogeneous White Emulsion	Homogeneous White Emulsion	Homogeneous White Emulsion	Homogeneous White Emulsion	Homogeneous White Emulsion	Homogeneous White Emulsion	Homogeneous White Emulsion	Homogeneous White Emulsion	Homogeneous White Emulsion
Specific Gravity	0.980	0.980	0.980	0.980	0.980	0.980	0.980	0.980	0.980
pH	3.90	3.95	3.90	3.15	3.00	2.85	2.8	2.45	2.40

Viscosity	2,518cps	2,532cps	2,730cps	2,420cps	2,320cps	2,400cps	2,390cps	2,230cps	2,160cps
Abamectin	0.097%	0.097%	0.097%	0.101%	0.101%	0.098%	0.096%	0.093%	0.093%
Albendazole	2.22%	2.23%	2.26%	2.26%	2.26%	2.22%	2.21%	2.25%	2.31%
Levamisole	3.75%	3.73%	3.72%	3.80%	3.86%	3.73%	3.69%	3.14%	3.02%

- LB99/01 has remained stable for 15 months under ambient and 30°C conditions. A pH drop has been noted.
- LB99/02 has remained stable for 15 months under ambient and 30°C conditions although the sample at 30°C is showing indications that Levamisole content may be starting to fall.
- LB99/03 has remained stable for 9 months under ambient and 30°C conditions but a significant drop in pH and Levamisole (19.5%) is evident at 15 months.
- These trials further indicate that pH stabilisation is desirable for long term stability.

pH STABILISATION TRIALS:

It is evident from the trends previously noted that some form of pH stabilisation is desirable (if not necessary).

A series of accelerated trials was carried out on a Triclabendazole, Abamectin and Levamisole formulation to study the effects of;

1) Chelated Minerals on pH stability.

2) Citrate Acid/Sodium Citrate buffer system on pH stability.

The trial formulations were stored at ambient and 40°C and pH tested regularly for 3 months.

Table 10 - Formulation Details for pH Stability Trial

	LB99/54A Mineralised No Buffer	LB99/54B Unmineralised No Buffer	LB99/54C Mineralised Buffered	LB99/54D Unmineralised Buffered
Soybean Oil	40.000%	40.000%	40.000%	40.000%
Ethoxylated Caster Oil	5.000%	5.000%	5.000%	5.000%
Abamectin @ 90%	0.110%	0.110%	0.110%	0.110%
Benzyl Alcohol	0.750%	0.750%	0.750%	0.750%
Triclabendazole @ 100%	2.500%	2.500%	2.500%	2.500%
Terasperse 4896	1.000%	1.000%	1.000%	1.000%
Terasperse 2500	2.000%	2.000%	2.000%	2.000%
Levamisole HCl @ 100%	3.750%	3.750%	3.750%	3.750%
Cobalt - EDTA	1.570%	--	1.570%	--
Sodium Selenate	0.120%	--	0.120%	--
Citric Acid	to pH 3.5	to pH 3.5	1.000%	1.000%
NaOH	--	--	to pH 3.5	to pH 3.5
Propylene Glycol	3.000%	3.000%	3.000%	3.000%
Xanthan Gum	0.250%	0.250%	0.250%	0.250%
Water to volume	As Required	As Required	As Required	As Required

Table 11 - Results: pH with time for compositions of Table 10. Ambient and 40°C

Temperature. Ambient Humidity

Age (Days)	99/54A @ Ambient	99/54A @ 40°C	99/54B @ Ambient	99/54B @ 40°C	99/54C @ Ambient	99/54C @ 40°C	99/54D @ Ambient	99/54D @ 40°C
0	3.50	3.50	3.50	3.5	3.5	3.50	3.50	3.50
3	3.57	3.61	2.90	2.97	3.55	3.55	3.51	3.55
6	3.62	3.65	2.90	2.70	3.55	3.45	3.51	3.45
10	3.84	3.95	2.87	2.39	3.60	3.61	3.50	3.50
13	4.01	3.71	2.84	2.29	3.62	3.56	3.52	3.51
18	4.06	3.64	2.86	2.27	3.66	3.61	3.51	3.50
21	3.91	3.70	2.80	2.31	3.60	3.60	3.51	3.51
28	4.16	3.90	2.90	2.34	3.60	3.60	3.50	3.62
60	4.25	4.22	2.85	2.25	3.60	3.55	3.50	3.60
90	4.27	4.23	2.79	2.16	3.55	3.60	3.50	3.66

See Figure 16 for stability graph of pH change with time.

Conclusions and Recommendations:

Some of the early batches of the present invention have shown a trend of significant pH changes with time. Mineral chelates also appear to affect the direction the pH change occurs, ie; with mineral chelates pH increases and without these pH decreases. In either case this is likely to have detrimentally effects on the stability of Levamisole which is normally expected around pH 3.0 to 4.0. Therefore some method of pH stabilising is desirable (if not necessary) for longer term stability.

The Citric Acid/Sodium Citrate system which uses Citric acid/sodium hydroxide (NaOH) appears suitable for this purpose in these formulations. Other pH stabilising systems (such as the Phosphate buffer system) have also been considered.

Comparative Accelerated Stability

A study to compare the relative stability of a number of the formulations within the invention with standard commercial formulations at very high temperature (50°C) was conducted. The commercial formulations used have shelf-lives of 2 years or more. Six test formulations (A, B, C, D, E and J) and 4 commercial formulations consisting of 3 single active drenches (F, G, H) and 1 triple active drench (I) were placed under identical conditions, including identical high density polyethylene containers and identical closure systems and placed in a 50°C oven at ambient humidity. In the test formulations of the invention used either abamectin or ivermectin triple active formulations, with or without minerals, buffered or unbuffered, and one had the addition of praziquantel (E). These are detailed in Table 12 and 13.

SUMMARY OF DRENCH PRODUCTS PLACED ON ACCELERATED (50°C AMBIENT HUMIDITY) STABILITY:

Table 12:

DRENCH	DESCRIPTION
A	Abamectin Triple, plain, unbuffered, 20% higher active content
B	Abamectin Triple, plain, buffered
C	Ivermectin Triple, plain, buffered
D	Ivermectin Triple, mineralised, buffered
E	Ivermectin Quad, mineralised, buffered
F	IVOMEC™ sheep drench (Ivermectin)
G	NILVERM™ drench (Levamisole)
H	VALBAZEN™ drench (Albendazole)
I	FIRST DRENCH™ (Albendazole, Praziquantel, Levamisole, mineralised)
J	Abamectin Triple, mineralised, buffered

Formulations A, B, C, D, E and J are formulations of the present invention.

Table 13: Formulation details for Test Products used in Accelerated Stability (50°C)

	E	D	C	J	B	A
Material (%) Content	**2.00% Albendazole 3.00% Levamisole 1.50% Praziquantel 0.08% Ivermectin Minerals**	**2.00% Albendazole 3.00% Levamisole 0.08% Ivermectin Minerals**	**2.00% Albendazole 3.00% Levamisole 0.08% Ivermectin**	**2.00% Albendazole 3.00% Levamisole 0.08% Abamectin Minerals**	**2.00% Albendazole 3.00% Levamisole 0.08% Abamectin**	**2.50% Albendazole 3.75% Levamisole 0.10% Abamectin Unbuffered**
Soybean oil	40.000	40.000	40.000	40.000	40.000	40.000
Teric 3800	5.000	5.000	5.000	5.000	5.000	5.000
Ivermectin @ 90%	0.088	0.088	0.088	N/A	N/A	N/A
Abamectin @ 90%	N/A	N/A	N/A	0.088	0.088	0.088
Benzyl alcohol	1.500	1.500	1.500	1.500	1.500	1.500
Albendazole @ 99%	2.020	2.020	2.020	2.020	2.020	2.020
Terasperse 4896	1.000	1.000	1.000	1.000	1.000	1.000
Terasperse 2500	2.000	2.000	2.000	2.000	2.000	2.000
Praziquantel @ 98.8%	1.518	N/A	N/A	N/A	N/A	N/A
Water	25.000	25.000	25.000	25.000	25.000	25.000
Levamisole HCL @ 99.5%	3.015	3.015	3.015	3.015	3.015	3.015
Propylene glycol	3.000	3.000	3.000	3.000	3.000	3.000
Cobalt Chelate	1.260	1.260	N/A	1.260	N/A	N/A
Sodium Selenate	0.096	0.096	N/A	0.096	N/A	N/A
Keltrol F	0.200	0.200	0.200	0.200	0.200	0.200
NaOH (Tp pH 3.75)						
Citric acid	1.000	1.000	1.000	1.000	1.000	N/A
Water to volume						

- See Figure 19 which is a plot of mean droplet/particle size against time.

POINTS TO NOTE REGARDING 4 WEEK ACCELERATED (50°C AMBIENT HUMIDITY) STABILITY RESULTS:

- pH change greatest for the unbuffered drench A, no other significant differences (Figure 17). The change in pH for all products was greatest in the first two weeks (especially after the first week). However, the changes in pH have not impacted on the physical or chemical stability of any of the formulations. The lack of buffering agent in drench A has not affected the stability of this drench relative to the others, at least not in the short term.
- Viscosity decrease was greatest in quad drench E, which started out with the highest initial viscosity (Figure 18). Correlates well with the observed particle size increase (Figure 19). The triple formulations of the present invention showed the best stability with respect to viscosity. In the test formulations the particles measured would predominantly be the oil droplets/particles.
- Drench F (IVOMEC™) has a very low viscosity (>100 x less than preferred formulations of the present invention), hence stability related decreases are not expected to be significant
- No significant trend in moisture content is apparent (Figure 20). The low values for A and B are due to the variability of the measurement technique – as seen on the weekly summary graph. The stability of the moisture content and the physical observations of the integrity of the containers (no change from initial) indicates that the packaging and closure system is adequate for the formulation products of the present invention in the short term at high temperature.
- Levamisole loss is consistent at around 10% for all of the drench products (Figure 21). Initial loss of active was rapid (from initial to 1 week through to 2 weeks) but then stabilised.
- No significant change in Praziquantel levels was observed (Figure 22).
- No significant change in Albendazole levels was observed. (Figure 23).

- The % Albendazole change for Drench H (VALBAZEN™) was calculated from week 2 to week 4, as the initial results appear to be erroneous.
- The Ivermectin (Figure 24) and abamectin (Figure 25) appears stable with similar trends between formulations and no obvious loss of active. The 1 week ivermectin result for drench D appears to have been erroneous.
- Benzyl alcohol loss (Figure 26) is consistent across all the products. Drench F (IVOMEC™ sheep drench) has twice the level of benzyl alcohol than the formulations of the present invention and also twice the water content.
- Selenium (Figure 27)and cobalt (Figure 28) levels in the mineralised drenches show no significant changes over the four week period.

CONCLUSION:

After four weeks of storage at 50°C, ambient humidity:

- The formulations of the present invention show physical and chemical stability that is

at least as good as products F, G, H and I available on the New Zealand market

- There is no difference in the physical or chemical stability of the Ivermectin products

versus the abamectin products in formulations of the present invention.

PARTICULATE CONTENT:

The stability of the formulation when albendazole particles were removed and substituted with Silicon dioxide and titanium dioxide particles was tested in the following formulations. These were used as pour-on formulations in cattle.

A) Pour-on, Injectable and Gel Formulations:

Formulations were developed with higher loading of actives, substituting and loading particulate content using silicon dioxide and titanium dioxide. These formulations were developed to be used as pour-ons, injectible or as oral gels.

The following formulations were prepared.

LB99/96A – 0.5% Ivermectin + 1% Silicon Dioxide

LB99/96B – 0.5% Ivermectin + 1% Silicon Dioxide + 2.0% Titanium Dioxide as a UV screen.

LB99/96C – 0.5% Ivermectin + 10.0% Levamisole + 1% Silicon Dioxide with 2.0% Titanium Dioxide.

LB99/72A – 0.1% Ivermectin, 3.75% Levamisole, 1.88% Praziquantel with 8% Silicon Dioxide.

Table 14 - Ivermectin, Ivermectin/Levamisole and Ivermectin/Levamisole/Praziquantel

Formulations With Silicon Dioxide and Titanium Dioxide Added

Material	LB99/96A	LB99/96B	LB99/96C	LB99/72A
Soybean Oil	40.00%	40.00%	40.00%	15.00%
Teric 380	5.00%	5.00%	5.00%	5.00%
Ivermectin @ 100%	0.50%	0.50%	0.50%	0.10%
Benzyl Alcohol	5.00%	5.00%	5.00%	1.50%
Levamisole HCl @ 100%	-	-	10.00%	3.75%
Colloidal Silicon Dioxide	1.00%	1.00%	1.00%	8.00%
Praziquantel	-	-	-	1.88%
Titanium Dioxide	-	2.00%	2.00%	-
Propylene Glycol	3.00%	3.00%	3.00%	-
NaOH (to pH 3.5)	0.21%	0.22%	0.39%	0.37%
Xanthum Gum	0.50%	0.50%	0.10%	-
Citric Acid	1.00%	1.00%	1.00%	1.00%
Water to volume	To volume	To volume	To volume	To weight
Appearance	Off white fluid which separates on standing	White fluid which separates on standing	Homogeneous white fluid	Homogeneous white gel
pH	3.5	3.5	3.5	3.5
Viscosity %	1,600cps	1,800cps	3,100cps	>100,000cps

Note that Colloidal Silicon Dioxide was added to the formulation as a substitute for the solid component (such as Albendazole, Oxfendazole and Triclabendazole) that might desirably be found in the oral formulations. Titanium Dioxide filled a similar function to such benzimidazole solids insofar as stability is concerned as well as an UV screen.

Observations:

The solid component in LB99/96A and LB99/96B rapidly settled after agitation even though both formulations had five times as much Xanthan gum as LB99/96C. LB99/96C's higher viscosity and superior suspension properties is attributed to an interaction of Xanthan gum with the chloride portion of Levamisole Hydrochloride. See Figure 29.

Formulation LB99/96C was also considered suitable for an injectable formulation but ideally would have the silicon dioxide/titanium dioxide substituted with a readily biodegradable/metabolised particle and the levamisole hydrochloride substituted by levamisole phosphate to be less irritant at the injection site.

Formulation LB99/72A formed a white thick pourable gel which was considered to have application for example orally in horses, dogs and cats.

B) Water Tolerance:

Test - The pour-on formulations listed in Table 14 (LB99/96A, LB99/96B and LB99/96C) were mixed with 10% extra water and any effect observed.

Result - No gelling. The additional water and drench phase mixed cleanly and no other reaction observed. This was also confirmed in other formulations including Example 12.

C) Drenchability:

Test - Formulations of the present invention (such as LB 99/96A, LB99/96B and LB99/96C of Table 14) were applied though a standard drench gun containing residual water.

Result - Again no gelling occurred and the gun operated smoothly. Drenches of the present invention are unlikely to negatively affect the performance of the drench guns. The presence of oil in the formulation would likely act as a lubricant.

FREEZE/THAW TRIALS:

The physical characteristic of drenches of the present invention when repeatedly frozen and then thawed was investigated. A series of Triclabendazole, Abamectin and Levamisole drenches, LB99/52A to LB99/52G (see Table 15) were formulated and was cycled between minus 4°C (- 4°C) and ambient conditions daily for 4 days. Their response to these conditions was compared to that of a number of current standard suspension drenches; SYSTAMEX™, VALBAZEN™ and FIRST DRENCH™.

Table 15 - Test Formulations Used in Freeze Thaw Trials

Material	LB99/52A	LB99/52B	LB99/52C	LB99/52D	LB99/52E	LB99/52F	LB99/52G
Soybean Oil	40.00%	40.00%	40.00%	40.00%	40.00%	40.00%	40.00%
Teric 380	5.00%	5.00%	5.00%	5.00%	5.00%	5.00%	7.50%
Abamectin @ 100%	0.10%	0.10%	0.10%	0.10%	0.10%	0.10%	0.10%
Benzyl Alcohol	0.75%	0.75%	0.75%	0.75%	0.75%	0.75%	0.75%
Triclabendazole@100%	2.50%	2.50%	2.50%	2.50%	2.50%	2.50%	2.50%
Terasperse 4896	1.00%	1.00%	1.00%	1.00%	1.00%	1.00%	1.00%
Terasperse 2500	0%	1.00%	2.00%	3.00%	4.00%	2.00%	2.00%
Levamisole HCl @ 100%	3.75%	3.75%	3.75%	3.75%	3.75%	3.75%	3.75%
Cobalt - EDTA	1.57%	1.57%	1.57%	1.57%	1.57%	0%	1.57%
Sodium Selenate	0.12%	0.12%	0.12%	0.12%	0.12%	0%	0.12%
Propylene Glycol	3.00%	3.00%	3.00%	3.00%	3.00%	3.00%	3.00%
Keltrol F	0.3%	0.30%	0.30%	0.30%	0.30%	0.30%	0.30%
Citric Acid	0.1%	0.10%	0.10%	0.10%	0.10%	0.10%	0.10%
Water to volume	As Required	As Required	As Required	As Required	As Required	As Required	As Required

LB99/52C is considered a "standard" with 1.0% Terasperse 4896, 2.0% Terasperse 2500, 5.0% Teric 380 and minerals.

LB99/52A as per standard but no Terasperse 2500.

LB99/52B as per standard but 1.0% Terasperse 2500.

LB99/52D as per standard but 3.0% Terasperse 2500.

LB99/52E as per standard but 4.0% Terasperse 2500.

LB99/52F as per standard but no minerals.

LB99/52G as per standard but 7.5% Teric 380.

RESULTS - Table 15 Formulations

200mL's of each formulation was stored in clear 250mL glass bottles and examined for separation, homogeneity and sediment. These results are also presented in graph form in Figure 30.

Terminology in Table 16

Sep ↑ or Separation top– mL's of clear material forming separate **above** any suspended material or sediment.

Sep ↓ or Separation Bottom– mL's of clear material forming separate **below** any suspended material.

Hm or Homogeneous – no indication of settling or sedimentation.

Table 16

	LB99/52A	LB99/52B	LB99/52C	LB99/52D	LB99/52E	LB99/52F	LB99/52G	Systamex	Valbazen	First Drench
Day 1	Hm	Hm	Hm	Sep ↓ 2mLs	Sep ↓ 2mLs	Hm	Sep ↓ 2mLs	Hm	Sep ↑ 25mLs	Sep ↑ 50mLs
Day 2	Hm	Hm	Sep ↓ 1mLs	Sep ↓ 5mLs	Sep ↓ 5mLs	Sep ↓ 1mLs	Sep ↓ 5mLs	Hm	Sep ↑ 25mLs	Sep ↑ 50mLs
Day 3	Sep ↓ 3mLs	Sep ↓ 3mLs	Sep ↓ 5mLs	Sep ↓ 10mLs	Sep ↓ 10mLs	Sep ↓ 5mLs	Sep ↓ 20mLs	Hm	Sep ↑ 30mLs	Sep ↑ 50mLs
Day 4	Sep ↓ 5mLs	Sep ↓ 4mLs	Sep ↓ 12mLs	Sep ↓ 20mLs	Sep ↓ 25mLs	Sep ↓ 12mLs	Sep ↓ 70mLs	Hm	Sep ↑ 5mLs	Sep ↑ 50mLs

See Figure 30.

Discussion:

The following trends were evident;

1) Increasing the surfactant content (Teric 380 and Terasperse 2500) in a formulation of the present invention decreases it's physical stability under severe freeze thaw conditions.

2) Minerals have no noticeable effect on freeze/thaw properties.

3) Drenches of the present invention differ from standard suspension drenches in the way they separate. Standard drenches separate to form a clear layer on top, while drenches of the invention form a similar layer on the bottom. This may be due to density. Suspended solids are usually heavier than water and may sink, while oil-based emulsions, as in drenches of the present invention, are usually lighter than water and may remain in the top portion. In physically unstable formulations of the present invention there is a top phase of oil, a middle phase of suspended solids, and a bottom water layer phase. This is illustrated as A in Figure 31. This contrasts with the physically stable formulation (B of Figure 31) which remained homogeneous.

4) A standard formulation of the present invention containing 5.0% Teric 380 and 2.0% Terasperse 2500 appears to separate out less than VALBAZEN™ and FIRST DRENCH™ drenches.

5) All suspension drenches readily re-suspended with minimal agitation.

6) All drenches of the present invention readily re-emulsified with minimal agitation.

7) After storage in the freezer all drenches froze solid. The drenches of the present invention melted significantly faster than the traditional suspension drenches. Drenches of the present invention were fluid in less than 20 minutes while the suspension drenches took several hours.

Stability Conclusions

The results of the accelerated stability trials at 30°C for up to 19 months and comparative stability at 50°C for 1 month, demonstrate that within the invention there are formulations with multiple actives that are chemically and physically stable including combinations of previously incompatible actives such as the ML's (ivermectin, abamectin) and Levamisole. In addition, the freeze/thaw trials, water tolerance, substitution and loading of actives demonstrate these are versatile and robust formulations suitable for field use. The presence of particulate matter, a suitable buffering system to maintain a stable acid pH, the presence of suitable and appropriate amounts of thickening agents, emulsifiers and oil have also been shown to determine the stability of these formulations. Surprisingly, increasing amounts of emulsifying agents were found to increase the physical instability and phase separation with freeze/thawing. The presence of a particulate material (such as a benzimidazole) and also levamisole hydrochloride was found to contribute positively to physical stability. Additionally not only were formulations found to be very versatile, capable of holding four actives simultaneously in one stable formulation, but the suspoemulsion's physical characteristics overcome some problems associated with current commercial suspensions. For example, in current benzimidazole suspensions, the particles with time settle and stick to the bottom of containers and are difficult to resuspend. This can affect the concentration and amount of active dosed. In the current invention, the particles settle toward the middle liquid layer not the bottom and so particles are readily available for resuspension.

The oil within the formulation also acts as lubricant in the drench gun. It is common farming practice to leave drench guns to sit with traditional suspensions within them. Over time there is settling out of particles and a drying out of the product including around the plunger. This can result in the particulate material abrading and damaging the drench gun when reused. In the current invention, the oil keeps the drench gun lubricated, making such damage less likely.

Animal Trials Overview

The following animal trial data in cattle and sheep demonstrates that when given orally the combination of anthelmintics in the experimental formulations appears equally bio-available based on blood profiles (Trials NC001, NC002), when compared with

commercial standard formulations alone, and this is supported by the egg count and worm kill data.

The benefits of combining previously incompatible actives together in one formulation is also demonstrated, with greater control of resistant or dose limiting gastro intestinal worms under experimental and field conditions. This benefit is demonstrated both with the oral formulations in sheep (Trials C052 and C0040) and as a pouron (Trial C012-400) in cattle.

In addition, mathematical models suggest there are long term benefits in the use of combination products with three or more actives from different action families both in extending and preserving the life of currently known anthelmintic or biocidal compounds.

ANIMAL TRIALS

- **Cattle Pilot Study (NC 001) - Oral and Pour-on Treatment**

Thirteen mixed breed weaner beef cattle (90-153 kg) from Northern New South Wales, Australia naturally infected with gastrointestinal roundworms were divided into four treatment groups by weight and nematode faecal egg count (FEC) into three groups of three animals and a fourth group of four animals.

Animals in group 2 were treated with the test combination formulation orally (Batch LB99/03, see example 15) at a dose of 1mL per 5 kg bodyweight. Group 3 of four animals had the same product (Batch LB99/03) applied as a pour-on along the midline of the upper back at a dose of 1 mL per 2.5 kg bodyweight. Group 4 received the same dose rate of the three actives as in group 2 given orally using three separate commercial formulations. Group 1 received no treatment (untreated control animals).

Animals were treated at Day 0 of the trial. Faeces for faecal egg count and blood samples for blood levels of active were collected at various times following treatment. Slaughter was at Day 14 of the trial where the total number of worms were counted in the gastrointestinal tract.

The results are presented below and in the drawings.

Table 17 - Treatment Groups

Group	No. of Animals	Treatment	Route	Conc (Active)	Batch No.	Dose
1	3	No Treatment				
2	3	Combination Test Formulation (Example 15) Abamectin Oxfendazole Levamisole	Oral	 1.0g/L 22.6g/L 37.5g/L	 LB99/03	 1mL/5kg
3	4	Combination Test Formulation (Example 15) Abamectin Oxfendazole Levamisole	Pour On	 1.0g/L 22.6g/L 37.5g/L	 LB99/03	 1mL/2.5kg
4	3	Commercial Formulations Virbamec (abamectin) Systamex (oxfendazole) Young's Levamisole (levamisole)	 Oral Oral Oral	 0.8g/L 90.6g/L 37.5g/L	 33245 V2 153 MV-5-004 3183	Per Label

RESULTS

Table 18 - Faecal Egg Counts (strongyle eggs/gram)

Group	Treatment	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 13
1	Nil (Untreated control)	685	439	811	521	380	311	208	249	249	272
2	Oral Combination Formulation (Example 15)	491	2	0	0	0	0	0	0	0	0
3	Pour-on Combination Formulation (Example 15)	441	10	0	0	0	0	0	0	0	0
4	Oral Commercial Formulations	701	2	0	0	0	0	0	0	0	0

Treatment Day = Day 0

Table 19 - Total Worm Count - Individual Animal Data

Group	Treatment	Animal No.	Haemonchus placei	Trichostongylus axei	Ostertagia ostertagi	Cooperia Spp.	Oesophagostomum radiatum
1	Untreated	3100	440	1240	340	1900	29
1	Untreated	3101	340	140	3140	2240	6
1	Untreated	3102	220	0	1120	3340	76
2	Oral Comb	3103	0	0	0	0	0
2	Oral Comb	3104	0	0	0	0	0
2	Oral Comb	3105	0	0	0	0	0
3	Pour-on Comb	3106	0	0	0	0	0
3	Pour-on Comb	3107	0	0	0	0	0
3	Pour-on Comb	3108	0	0	0	0	0
3	Pour-on Comb	1079	0	0	0	0	0
4	Oral Comm	3109	0	0	0	0	0
4	Oral Comm	1077	0	0	0	0	0
4	Oral Comm	1078	0	0	0	0	0

In the drawings

Figure 1 is a plot of Avermectin B1a blood levels (ng/mL) against time (hours) for the different modes of administration,

Figure 2 is a plot of Levamisole blood levels (µg/ml) against time (hours) for the different modes of administration,

Figure 3 is a plot of Oxfendazole blood levels (µg/ml) against time (hours) for the different modes of administration, and

Figure 4 is a plot of Fenbendazole blood levels (µg/ml) against time (hours) for the different modes of administration.

RESULTS

The trial confirmed that the combination formulation (example 15, Batch LB99/03) was a highly effective anthelmintic in cattle both orally and as a pour-on. This is

demonstrated by a complete (100%) reduction in faecal egg count, two days following treatment and a greater than 99.9% reduction of gastrointestinal nematodes compared with untreated controls.

The blood profiles of abamectin, levamisole and oxfendazole with the test product (example 15) given orally were essentially similar to those achieved in animals receiving the three commercial formulations of these actives. The higher blood levels of oxfendazole in the combination product were probably because of the oily nature of the formulation. Such differences have been seen previously between oily and aqueous benzimidazole formulations (Hennessy 1996). The blood profiles in pour-on treated animals shows that levamisole blood levels were similar to those achieved orally, the abamectin were ten times lower than with the commercial oral abamectin formulation and low levels of oxfendazole and fenbendazole (a metabolite) were detected in blood.

- **Sheep Pilot Study (NC 002) - Oral Treatment**

Nine 17-20 month old merino hoggets from Northern New South Wales, Australia naturally infected with gastrointestinal roundworms were allocated on the basis of parasite faecal egg count (FEC) to 3 treatment groups of 3 animals, each group having a similar mean FEC.

At treatment day (day 0) animals in Group 1 received no treatment (untreated controls), Group 2 received the combination product orally as detailed in example 14 (Batch No. LB99/01) and Group 3 received the same dose of actives using 3 separate commercial formulations (abamectin, levamisole and albendazole) given orally.

Faeces for parasite FEC and blood for blood levels of active were collected at various times following treatment (day 0). Animals were slaughtered at day 14 following treatment, with total numbers of worms counted within the gastrointestinal tract.

The results are presented below and in the drawings.

Table 20 - Treatment Groups

Group	No. of Animals	Treatment	Route	Conc (Active)	Batch No.	Dose
1	3	No Treatment (controls)				
2	3	Abamectin Albendazole Levamisole	Oral	1.0g/L 23.8g/L 37.5g/L	LB99/01	1mL/5kg
3	3	Virbamec (abamectin) Valbazen (albendazole) Young's Levamisole (levamisole)	Oral	0.8g/L 19g/L 37.5g/L	33425 V2 7003 3183	Per Label

Results

Table 21 - Faecal Egg Counts (Strongyle Eggs/gram)

Group	Treatment	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 13
1	Nil	2205	2093	2543	1198	1930	3078	1351
2	Oral Combination Formulation (Example 14)	2213	722	0	0	0	0	0
3	Oral Commercial Formulations	2475	150	0	0	0	0	0

Table 22 - Total Worm Counts - Individual Animal Data

Abomasal Nematodes

Group	Treatment	Animal No.	Haemonchus contortus	Ostertagia circumcincta	Trichostrongylus axei
1	Nil	1	760	720	580
1	Nil	2	80	2220	840
1	Nil	3	180	1520	560
2	Oral Comb	4	0	0	0
2	Oral Comb	5	0	0	0
2	Oral Comb	6	0	0	0
3	Oral Comm	7	0	0	0
3	Oral Comm	8	0	0	0
3	Oral Comm	9	0	0	0

Table 23 - Total Worm Counts - Individual Animal Data

Small and Large Intestine Nematodes

Group	Treatment	Animal No.	Cooperia Spp.	Nematodirus spathiger	Trichostrongylus colubriformis	Oesophagostomum columbianum
1	Nil	1	340	1480	8260	144
1	Nil	2	760	1760	6040	137
1	Nil	3	60	1540	4800	134
2	Oral Comb	4	0	0	0	0
2	Oral Comb	5	0	0	0	0
2	Oral Comb	6	0	0	0	0
3	Oral Comm	7	0	0	0	0
3	Oral Comm	8	0	0	0	0
3	Oral Comm	9	0	0	0	0

In the drawings

Figure 5 is a plot of Avermectin B1a blood level (ng/mL) against time (hours) for the oral combination against a commercial oral formulation,

Figure 6 is a plot of Levamisole blood level (μg/ml) against time (hours) for the oral combination against a commercial oral formulation, and

Figure 7 is a plot of Albendazole blood levels (μg/ml) against time (hours) for the oral combination against a commercial oral formulation.

Results

The trial confirmed that the combination formulation (example 14, Batch No. LB99/01) was a highly effective anthelmintic when given orally in sheep. This was demonstrated by a complete (100%) reduction in faecal egg count by day 2 and a greater than 99.9% reduction in all major worm species in the gastrointestinal tract.

The blood profiles of abamectin, levamisole and albendazole with the test product (example 14) were essentially similar to those achieved in animals receiving commercial formulations of the same three actives.

CATTLE POUR-ON TRIAL (C012-400)

- **Cattle**

Thirty Friesian and Friesian cross weaner beef cattle (113-189kg) naturally infected with gastrointestinal roundworms were randomly allocated into 5 treatment groups of 6 animals with mean faecal egg counts per group of 100-183 eggs per gram at treatment day.

One group (treatment A) remained as untreated controls, the other 4 treatment groups were treated with a pour-on formulation at Day 0 as described in Table 24 using a syringe held 3-5cm above the animal skin with the products applied along the midline of the back between the shoulder blades (withers) in a line approximately 15cm long. This area was chosen to prevent calves licking themselves and they were observed after pour-on treatment to ensure that licking of other calves, particularly the pour-on site, did not occur.

In this trial the benzimidazole (albendazole or oxfendazole) which is particulate and exists in the water phase had been substituted with fine particles of silicon dioxide ($Si0_2$) alone or in combination with titanium dioxide ($Ti0_2$). See Formulations LB 99/96A, LB 99/96B, LB99/96C illustrated in Table 14). This was to determine if titanium dioxide which is used in sunscreens could significantly protect the ivermectin in the formulation. Ivermectin is degraded by UV light. Additionally the ivermectin content was increased from 0.1% to 0.5% to reduce the volume that needed to be applied to the animal (1mL per 10kg liveweight). This also allowed a comparison with a commercial ivermectin formulation IVOMEC™ pour-on which has a similar concentration of ivermectin.

The animals were slaughtered at day 8 and faeces (for faecal egg count) and the abomasum (stomach) and small and large intestines were collected for total gastrointestinal roundworm count. The results are presented in Tables 25 and 26. There were insufficient numbers of large intestinal worms to allow comparison.

Table 24 - Treatment groups and formulation data

Treatment Groups

Group	No. of Animals	Treatment Controls	% or g/100mL Concentration	Dose Rate (mLs per kg bodyweight (BW)	Batch No.	Expiry or Manufacture Date
A	6	Controls				
B	6	Commercial Ivomec Pour-on (B) Ivermectin	 0.5%	1mL per 10kg	HJ11640	Exp 12-2001
C	6	Test Product C Ivermectin Silicon Dioxide	 0.5% 1%	1mL per 10kg	LB 99/96A	Date of Man 11/99
D	6	Test Product D Ivermectin Silicon Dioxide Titanium Dioxide	 0.5% 1% 2%	1mL per 10kg	LB 99/96B	Date of Man 11/99
E	6	Test Product E Ivermectin Levamisole hydrochloride Silicon Dioxide Titanium Dioxide	 0.5% 10% 1% 2%	1mL per 10kg	LB 99/96C	Date of Man 11/99

Results

Only the test pour-on formulation containing both ivermectin and levamisole (formulation LB 99/96C) significantly reduced the faecal egg counts in treated animals. The egg count in Group E reaching zero (100% reduction) at Day 8 post treatment. This can be explained by the greater *Cooperia* worm kill in the small intestine of this treatment group. *Cooperia* is a highly prolific egg producing worm. Of these pour-ons only the ivermectin and levamisole combination (formulation LB 99/96C) was highly effective in removing adult *Cooperia* with a 95% or greater reduction in *Cooperia* worm numbers compared with untreated controls.

Both the commercial ivermectin formulation and the three test ivermectin pour-on formulations (LB 99/96A, LB 99/96B and LB 99/96C) were highly effective against adult stages of the abomasal worm *Ostertagia*. Titanium dioxide did not provide any significant improvement in worm kill (based on comparison of worm kill between formulation LB 99/96A and LB 99/96B). There was no significant skin or hair changes observed at the pour-on skin site suggesting the formulations were well tolerated and suitable as pour-on formulations. Observations of the formulations at the time of pour-on application were

that pour-on formulations LB 99/96A and LB99/96B both appeared physically unstable with rapid separation of the formulation. This was not true of the ivermectin and levamisole formulation (LB 99/96C) which remained homogeneous. See photo Figure 17. This was an unexpected observation. In this trial the addition of levamisole hydrochloride to the test ivermectin pour-ons significantly extended the spectrum of activity of the pour-on to include C*ooperia* and also appears to contribute to the formulations physical stability.

POUR-ON CATTLE TRIAL (CO12-400)

Table 25 - Liveweight, Dose Rate and FEC Data

Treatment	ID	Liveweight (kg)	Dose (ml)	Faecal Egg Count (eggs per gram) Day -7 17-Nov	Day 0 23-Nov	Day 8 36860
A. Control	10	167		50	0	50
	14	165		500	400	1850
	63	166		0	100	100
	64	143		0	0	*
	65	116		200	200	100
	73	154		250	400	750
	Means			166	183	475
B. Ivomec Pour-on B Commercial Formulation Batch HJ11640 Exp 12-2001 Dose Rate 1mL/10kg	2	136	13.6	100	300	450
	7	134	13.4	150	150	1200
	11	189	18.9	250	250	250
	70	144	14.4	0	0	0
	71	152	15.2	350	550	1250
	74	150	15	450	250	450
	Means			216	250	600
C. Test Pour-on C (Ivm/SiO_2) Formulation LB 99/96A 1mL/10kg	8	167	16.7	150	50	0
	67	154	15.4	250	400	*
	68	118	11.8	650	300	2600
	69	157	15.7	150	0	0
	72	122	12.2	200	350	600
	202	124	12.4	0	0	0
	Means			233	183	533
D. Test Pour-on D (Ivm/$TiO2/SiO_2$) Formulation LB 99/96B Dose Rate 1mL/10kg	3	176	17.6	550	100	450
	4	113	11.3	200	0	*
	6	144	14.4	350	350	100
	9	136	13.6	200	400	250
	12	149	14.9	50	0	0
	75	148	14.8	250	0	850
	Means			266	141	275
E. Test Pour-on (Ivm/Lev/$Ti0_2/Si0_2$) Formulation LB 99/96C 1ml/10kg	1	138	13.8	50	0	0
	5	152	15.2	500	50	0
	13	154	15.4	750	200	*
	61	157	15.7	1000	300	0
	62	183	18.3	150	0	0
	66	145	14.5	150	50	0
	Means			433	100	0
Means	1	Control		166	183	475
	2	Ivomec Pour-on B		216	250	600
	3	Test Pour-on C		233	183	533
	4	Test Pour-on D		266	141	276
	5	Test Pour-on E		433	100	0

* No faecal sample.

POUR-ON CATTLE TRIAL (CO12-400)

Table 26 - Worm Count Data

		Abomasum				Small Intestine	
		Ostertagia		Trichostrongylus axei		Cooperia	
	FEC (Day 8)	Mature	Immature	Mature	Immature	Mature	Immature
A. Controls							
10	50	1300	200	50	-	450	-
14	1850	2950	350	150	-	6500	1450
63	100	1300	350	150	-	1000	150
64		1000	50	-	-	3450	600
65	100	1350	100	-	-	2450	300
73	750	5650	300	-	-	18100	2250
Mean		2258	225	58		5325	792
B. Ivomec P.O.							
Batch # HJ11640							
2	450	-	-	-	-	3100	350
7	1200	-	-	-	-	3600	200
11	250	150	50	-	-	3000	100
70	0	-	-	-	-	1200	100
71	1250	50	-	-	-	7300	500
74	450	150	-	-	-	2600	400
Mean	600	58	8.3	0		3466	275
C. Test P.O. IVM + SiO_2							
Batch # LB 99/96A							
8	0	50	-	-	-	800	-
67	-	50	-	-	-	12300	150
68	2600	400	-	-	-	3500	-
69	0	50	-	-	-	2000	-
72	600	-	50	-	-	2550	-
202	0	50	-	-	-	400	50
Mean	533	100	8.3	0		3592	33
D. Test P.O. IVM+TiO_2+SiO_2							
Batch # LB 99/96B							
3	450	100	50	-	-	6800	250
4	-	-	-	-	-	2300	50
6	100	50	-	50	-	2500	-
9	250	-	200	50	-	3800	-
12	0	200	200	150	-	4000	50
75	850	-	-	-	-	750	-
Mean	275	58	75	41.6		3358	58
E. Test P.O. IVM/LEV+TiO_2+SiO_2							
Batch # LB 99/96C							
1	0	-	-	-	-	100	-
5	0	200	-	50	-	350	50
13		150	50	200	-	50	-
61	0	-	-	-	-	100	50
62	0	-	-	-	-	200	-
66	0	250	50	100	-	-	50
Mean	0	100	16.6	58	-	133	25
Efficacy % B	0	97.4	96.3	100	-	35	65
Arithmetic C	0	95.6	96.3	100	-	33	96
D	42	47.4	66.6	28	-	37	93
E	100	95.6	92.6	0	-	97.5	96.8
Efficacy % B		98.3	98.7			0	0
Geometric C		95	98.7			20.7	96.2
D		98.3	89.5			0.1	92
E		97.8	96.6			94.8	93.8

SHEEP TRIAL (CO52)

An anthelmintic drench trial was conducted on a sheep farm in North Auckland, New Zealand using 67 Romney and Romney cross suffock lambs (18-35kg bodyweight) of mixed sex. The farm had a history of illthrift, scouring and lamb deaths consistent with gastrointestinal roundworm parasitism despite regular 4 weekly oral drenching.

The 67 lambs were randomly allocated by egg count into 4 groups of 10 lambs (Groups A, B, C, D) and 3 groups of 9 lambs (Groups E, F, G). The 3 groups of 9 lambs (E, F G) were drenched with a commercial formulation from one of the three broad spectrum anthelmintic drench families consisting of albendazole, a member of the benzimidazole or white drenches (Group E), levamisole, a member of the imidazothiazole / tetrahydropyrimidazole or clear drenches (Group F) and Ivermectin, a member of the macrocyclic lactones (Group G). Of the 4 remaining groups, Group A remained as untreated controls, Group B received the unmineralised test product (formulation 00-27C) containing all 3 actives (albendazole, levamisole, ivermectin), Group C received the same basic formulation but with the addition of selenium as the sodium selenate (formulation 00-27B) and Group D received the same basic formulation but with the addition of both selenium and cobalt with cobalt given as the cobalt chelate (formulation 00-27A) - See Table 27.

All animals were weighed and dosed by syringe to the nearest 0.1ml with the appropriate product for that group. Six days after oral treatment the animals were slaughtered and faecal samples were collected at slaughter. The liveweight, dose rates and faecal egg count data are presented in Table 28.

TEST

FORMULATIONS FOR SHEEP TRIAL (CO52):

Table 27:

	Theoretical %	Actual % (Adusted for potency)	00-27A 3 Litre Batch	00-27B 2 Litre Batch	00-27C 2 Litre Batch
			2.00% Albendazole 3.00% Levamisole 0.080% Ivermectin SeCo	2.00% Albendazole 3.00% Levamisole 0.080% Ivermectin Se	2.00% Albendazole 3.00% Levamisole 0.080% Ivermectin Plain
Soybean Oil	40.000	40.000	1200.00	800.00	800.00
Teric 380	5.000	5.000	150.00	100.00	100.00
Ivermectin @90%	0.080	0.088	2.64	1.76	1.76
Benzyl Alcohol	1.500	1.500	45.00	30.00	30.00
Albendazole @ 99%	2.000	2.020	60.60	40.40	40.40
Terasperse 4896	1.000	1.000	30.00	20.00	20.00
Terasperse 2500	2.000	2.000	60.00	40.00	40.00
Water	25.000	25.000	750.00	500.00	500.00
Levamisole HCl @ 99.5%	3.000	3.015	90.45	60.30	60.30
Propylene Glycol	3.000	3.000	90.00	60.00	60.00
Cobalt Chelate	1.260	1.260	37.80		
Sodium Selenate	0.096	0.096	2.88	1.92	
Keltrol F	0.200	0.200	6.00	4.00	4.00
NaOH (to pH 3.75)					
Citric Acid	1.000	1.000	30.00	20.00	20.00
Water to Volume	to 100 mL	N/A	to 3,000 mL	to 2,000 mL	to 2,000 mL

Results:

The egg counts at slaughter in the untreated animals and the less effective anthelmintics were considerably higher than at treatment day (Day 0). The most likely explanation for this is reduced volume and flow of intestinal contents. This is likely the result of reduced food intake and a greater colonic absorption of water because of yarding the previous day (Day 5) increasing the concentration of eggs per gram of faeces. Despite this, a comparison with the egg counts of the untreated control animals is valid and gave reductions in egg count of 79% for ivermectin, 63% for albendazole and only 22% for levamisole (based on arithmetic mean).

These egg count reductions suggest resistance to all 3 drench families and are well below reductions typically seen with these drench families in susceptible worm populations. All test combination formulations (00-27A, 00-27B, 00-27C) gave 100% reductions in egg count, with greater than 95% reduction considered to indicate a highly effective anthelmintic treatment.

This trial confirmed the benefits of combining all 3 actives in the test formulations.

This combination resulted in a highly effective anthelmintic drench, despite resistance being present on this farm to each of the 3 anthelmintic drench families when given separately.

Table 28 - Trial (CO52) - Faecal Egg Counts at Treatment Day and Day 6

Tag	Body-weight (kg)	Dose Rate (mL)	Egg Count (Day 0) (epg)	Egg Count (Day 6) (epg)	Tag	Body-weight (kg)	Dose Rate (mL)	Egg Count (Day 0) (epg)	Egg Count (Day 6) (epg)
A. Untreated					E. Albendazole (Abz) Valbazen Batch 51660 Exp Feb 2001 (1 mL per 5kg – 5.0mg/kg)				
1112	25.2		400	14200	526	21.7	4.3	300	2600
1113	21.5		200	100	527	20.7	4.1	0	700
1114	27.9		400	12100	528	20.2	4.0	200	1600
1115	28.3		100	3200	529	19.8	4.0	300	6800
1116	20.5		0	0	530	32.3	6.5	600	3100
1117	25.3		200	8000	532	20.6	4.1	100	4900
1118	30.7		0	2900	533	26.6	5.3	0	300
1119	24.6		100	16300	659	21.7	4.3	100	1700
1120	25.4		300	3700	660	24.7	4.9	200	0
1121	20.8		0	4200	Mean			200	2411 (63%)
Mean			170	6470					
B. Test Formulation Batch No. 00-27C (Ivm,Lev,Abz, Plain) (1 mL per 4kg – 200ug/7.5mg/5.0mg/kg)					F. Levamisole (Lev) Nilverm Batch 51930 Exp Nov 2004 (1 mL per 5.33kg - 7.5mg / kg)				
135	35.5	8.9	400	0	701	19.8	3.7	100	15500
136	15.8	4.0	100	0	702	24.0	4.5	100	1100
137	24.7	6.3	300	0	703	26.9	5.1	200	4300
139	21.9	5.5	0	0	704	22.4	4.2	0	3700
140	25.5	6.4	0	0	705	21.1	4.0	300	4700
141	29.9	7.5	800	0	706	31.0	5.8	500	200
142	23.0	5.8	200	0	707	23.2	4.4	200	3700
143	30.0	7.5	100	0	708	19.0	3.6	400	1400
144	24.0	6.0	600	0	834	24.7	4.7	0	10900
145	27.7	6.9	100	0	Mean			200	5055 (22%)
Mean			260	0 (100%)					
C. Test Formulation Batch No. 00-27B (Ivm, Lev, Abz, Se) (1 mL per 4kg – 200ug/7.5mg/5.0mg/kg)					G. Ivermectin (Ivm) Ivomec Batch Y8289 Exp Nov 2002 (1 mL per 4kg – 200ug/kg)				
176	33.8	8.5	200	0	876	25.5	6.4	100	0
177	23.6	5.9	0	0	877	24.7	6.2	300	700
178	24.9	6.2	300	0	878	29.4	7.4	200	0
179	21.3	5.3	200	0	879	25.0	6.3	0	0
180	18.2	4.6	400	0	880	24.0	6.0	300	600
181	19.6	4.9	600	0	881	32.1	8.0	100	0
182	26.5	6.6	900	0	882	19.8	5.0	800	100
183	24.2	6.0	0	0	883	29.9	5.7	0	11000
309	29.3	7.3	100	0	1008	28.4	7.1	400	0
310	29.5	7.4	100	0	Mean			244	1377 (79%)
Mean			280	0 (100%)					
D. Test Formulation Batch No. 00-27A (Ivm, Lev,Abz, SeCo) (1 mL per 4kg – 200ug/7.5mg/5.0mg/kg)									
351	25.0	6.3	300	0					
352	20.3	5.1	100	0					
353	25.3	6.3	100	0					
354	25.2	6.3	400	0					
355	23.1	5.8	200	0					
356	26.1	6.5	300	0					
357	22.6	5.7	300	0					
358	25.2	6.3	0	0					
484	29.0	7.3	700	0					
485	29.6	7.4	0	0					
Mean			240	0 (100%)					

epg = eggs per gram

TRIAL C0040 - SHEEP ROUNDWORM AND TAPEWORM TRIAL

Fifty three pasture fed 6-8 month old Romney lambs from the southern North Island, New Zealand that were naturally infected with tapeworms, were orally dosed with three times the standard dose of ivermectin (3 x 0.2 = 0.6mg/kg liveweight) to remove their naturally acquired roundworm infection while leaving their tapeworm burden. The animals were then housed indoors on slats to prevent natural reinfections with roundworms and each lamb was orally dosed daily for 5 days with a similar mixture of 5,000 roundworm larvae (total 25,000 larvae) consisting primarily of *Haemonchus*, *Trichostrongylus*, *Ostertagia* and *Nematodirus*. The larvae originated from four New Zealand sheep farms, three of which had evidence of resistance to one or more drench families. Lambs were injected with 0.5mL of a corticosteroid (opticortenol) two days prior to artificial oral larval infection. This was done to assist establishment of the worm larvae. 25 days after infection the animals were restrictively allocated to groups by bodyweight and also the presence of tapeworm infection, to one of seven treatment groups (Groups A-G). Four treatment groups (the untreated control and test products Groups A-D) had 8 animals per group, and three groups (E-G) contained 7 animals per group. The groups with 7 animals per group (E, F, G) were orally dosed with a single standard commercial product. All animals were slaughtered at Day 7 and Day 8 after treatment and total numbers of gastrointestinal roundworms and tapeworms counted. The treatment groups, liveweight and formulation and dose rate data are summarised in Table 29. The worm count data, including tapeworm data is summarised in Table 30.

Results

Roundworms

All products including the three test formulations (LC00/14, 99/99B, LB00/09) were highly effective (greater than 95% reduction in worm numbers) against *Haemonchus* except albendazole which reduced numbers by 93% (based on arithmetic means). The *Ostertagia* however showed greater resistance with only 54% removal of worm numbers with ivermectin alone and 64% removal by albendazole alone. Levamisole was still effective at 96% removal but the greatest removal (>99.9%) was achieved with the three combination test products.

Against *Nematodirus* in the small intestine, ivermectin and the three test products were fully effective (100% reduction), levamisole removed 99% of adult *Nematodirus* and albendazole removed only 59%.

All formulations were fully effective (100%) against *Trichostrongylus* in the small intestine except albendazole which was 80% effective.

Tapeworms

While there appeared to be a slight trend to less *Moniezia* volume in albendazole treated animals, only the test formulation LB00/09 with the addition of praziquantel was effective in removing the entire tapeworm (scolex and segments).

Conclusion

Levamisole alone and the combination test formulations (LB00/14, 99/99B, LB00/09) were highly effective against all roundworm species in this trial. Despite not having roundworms with marked resistance to levamisole, the three test formulations removed more worms than any of the single active commercial formulations alone indicating the benefits of combining the actives together in one single formulation. Additionally only the test formulation with praziquantel was effective in removing the tapeworm *Moniezia*.

TRIAL C0040

Table 29 – Tag Identification, bodyweight, formulation and dose rate

Tag I.D.	Weight (kg)	mL
A. Untreated Control		
218	18.3	-
6189	30.8	-
6163	34.2	-
6216	32.4	-
6197	32.6	-
6151	33.6	-
6221	34.2	-
6237	35.2	-
Mean	31.4	
B. Formulation LB00/14 Ivermectin, Levamisole, Albendazole (1mL per 4kg, 0.2mg, 7.5mg, 5mg/kg)		
6175	28.2	7.1
6236	30.4	7.6
6148	31.5	7.9
6183	32.2	8.1
6168	32.9	8.2
6241	33.5	8.4
6192	31.7	7.9
6156	30.4	7.6

Mean	31.4	
C. Formulation 99/98B Ivermectin, Levamisole, Albendazole, SeCo (1mL per 4kg, 0.2mg, 7.5mg, 5mg/kg)		
220	19.4	4.9
6174	35.0	8.8
6185	32.0	8.0
6226	32.4	8.1
6219	32.6	8.2
6182	33.1	8.3
6240	34.5	8.6
6166	35.5	8.9
Mean	31.8	
D. Formulation LB00/09 Ivermectin, Levamisole, Albendazole, Praziquantel, SeCo (1mL per 4kg, 0.2mg, 7.5mg, 5mg, 3.75mg/kg)		
221	25.4	6.4
6154	30.5	7.6
6232	31.0	7.8
6220	32.5	8.1
6152	32.9	8.2
6229	32.2	8.1
6202	33.4	8.4
6149	33.7	8.4
Mean	31.5	
E. Albendazole, Valbazen Batch #51660, Exp Feb 2001 (1mL per 5kg, 5mg/kg)		
6228	27.6	5.5
6203	31.0	6.2
6212	32.3	6.5
6195	33.0	6.6
6230	35.5	7.1
6190	35.7	7.1
6225	35.8	7.2
Mean	33.0	
F. Levamisole, Nilverm Batch #51930, Exp Nov 2004 (1mL per 5.3kg, 7.5mg/kg)		
6223	29.1	5.5
6217	30.1	5.6
6193	32.5	6.1
6207	33.6	6.3
6224	35.0	6.6
6208	35.8	6.8
6157	36.5	6.9
Mean	33.2	
G. Ivermectin, Ivomec Oral, Batch #8289, Exp Nov 2002 (1mL per 4kg, 0.2mg/kg)		
6171	30.1	7.5
6160	30.3	7.6
6239	31.0	7.8
6196	33.9	8.5
6170	35.2	8.8
6181	35.6	8.9
6199	36.6	9.2
Mean	33.2	

Trial C0040 - Table 30

Table Total abomasal and small intestinal roundworm and tapeworm count

	Abomasum			Small Intestine			
	Roundworm			Roundworm		Tapeworm	
Tag	Haemonchus	Ostertagia/T.Axei		Nematodirus	Trichostrongylus	Moniezia Scolex	Moniezia Volume (mL)
A:Control							
218	3650	3300	0	3150	5400	0	
6151	3850	3650	0	2750	3650	1	18
6163	4200	4750	50	2250	3900	4	120
6189	1150	250	0	1550	4200	1	<5
6197	2300	2600	0	100	2550	1	24
6216	2400	2700	50	1250	4300	1	31
6221	5800	3550	0	1600	2600	0	0
6237	1950	850	0	1000	4200	1	20
	Mean 3162	2706	12	1706	3850	1	36
B:Formulation LB00/14 Ivermectin, Levamisole, Albendazole (1mL per 4kg, 0.2mg, 7.5mg, 5mg/kg)							
6148	0	0	0	0	0	5	40
6156	0	0	0	0	0	1	9
6168	0	0	0	0	0	0	0
6175	0	0	0	0	0	1	
6183	0	0	0	0	0	0	0
6192	0	0	0	0	0	1	3
6236	0	0	0	0	0	1	<1
6241	0	50	0	0	0	1	
	Mean 0	7	0	0	0	1.2	10
C: Formulation 99/99B Ivermectin, Levamisole, Albendazole, SeCo (1mL per 4kg, 0.2mg, 7.5mg, 5mg/kg)							
220	50	0	0	0	0	3	6
6166	0	0	0	0	0	3	<1
6174	0	0	0	0	0	0	0
6182	0	0	0	0	0	0	0
6185	0	0	0	0	0	1	<1
6219	0	0	0	0	0	0	0
6226	0	50	0	0	0	3	31
6240	0	0	0	0	0	2	110
	Mean 6	6	0	0	0	2	24
D: Formulation LB00/09 Ivermectin, Levamisole, Albendazole, Praziquantel SeCo (1mL per 4kg, 0.2mg, 7.5mg, 5mg, 3.76mg/kg)							
221	0	0	0	0	0	0	0
6149	0	150	0	0	0	0	0
6152	0	0	0	0	0	0	0
6154	0	0	0	0	0	0	0
6202	0	50	0	0	0	0	0
6220	0	0	0	0	0	0	0
6229	0	0	0	0	0	0	0
6232	0	0	0	0	0	0	0
	Mean 0	25	0	0	0	0	0
E: Albendazole, Valbazen, Batch #51660, Exp Feb 2001 (1mL per 5kg or 5mg/kg)							
6190	100	1000	0	1000	1300	1	32
6195	100	1450	0	1200	450	1	2
6203	150	400	0	3250	200	0	0
6212	500	1450	0	2100	900	2	<1
6225	300	650	0	1950	600	2	
6228	250	1350	0	1750	350	1	32
6230	150	550	0	2300	1100	2	2
	Mean 221	979	0	1936	700	1	14
F: Levamisole, Nilverm, Batch #51930, Exp Nov 2004 (1mL per 5.3kg or 7.5mg/kg)							
6157	0	0	0	0	0	7	54
6193	0	200	0	0	0	1	
6207	0	450	0	100	0	3	35

6208	0	50	0	50	0	1	60
6217	0	0	0	50	0		<1
6223	0	0	0	0	0	5	9
6224	0	0	0	0	0	3	50
	Mean 0	100	0	29	0	3	42
G: Ivermectin, Ivomec Batch #8289, Exp Nov 2002 (1mL per 4kg or 0.2mg/kg)							
6160	0	1950	0	0	0	1	<1
6170	0	1700	0	0	0	0	0
6181	0	1000	0	0	0	0	0
6196	0	2200	0	0	0	3	<1
6199	0	750	0	0	0	1	33
6239	0	950	0	0	0	2	39
6171	0	250	0	0	0	6	57
	Mean 0	1257	0	0	0	1.9	26

WHAT IS CLAIMED IS:

1. **A pesticidal composition** comprising or including

(i) at least one active ingredient that is lipophilic in character,

(ii) at least one organic liquid carrier which carries at least most of the lipophilic active ingredient(s), thereby defining an organic liquid phase,

(iii) levamisole, and

(iv) at least water which carries at least most of said levamisole thereby defining an aqueous phase,

wherein said aqueous phase has a pH of less than 7,

and wherein there is present in said aqueous phase an emulsifying agent or agents,

and wherein said phases exist in, or can be shaken or agitated into, the form of an emulsion with said particulate content, if any, at least substantially present in the aqueous phase.

2. A composition of claim 1 wherein the lipophilic active ingredient is chosen from the class of macro cyclic lactones (hereafter "ML").

3. A composition as claimed in claim 1 or 2 wherein there is present in said aqueous phase a particulate content.

4. A composition as claimed in any one of the preceding claims wherein said aqueous phase has a pH of less than 6.

5. A composition of claim 4 wherein said aqueous phase has a pH of less than 5.

6. A composition as claimed in claim 5 wherein said aqueous phase has a pH of less than 4.

7. A composition as claimed in any one of the preceding claims wherein said aqueous phase includes a buffering system to buffer the pH.

8. A composition as claimed in claim 7 wherein said buffering system is a citric acid/citrate salt system.

9. A composition as claimed in any one of the preceding claims wherein said at least one organic liquid carrier is an oil.

10. A composition as claimed in claim 9 wherein said oil is a mineral or vegetable oil.

11. A composition as claimed in any one of the preceding claims wherein said organic liquid phase includes a co-solvent.

12. A composition as claimed in claim 11 wherein said co-solvent is benzyl alcohol.

13. A composition as claimed in any one of the preceding claims wherein said aqueous phase includes a particulate content of either an active agent or an inert substance.

14. A composition as claimed in claim 13 wherein the particulate active agent is a biocide.

15. A composition as claimed in any one of the preceding claims which includes in one or other, or both, of the partitioned phases one or more of the group comprising minerals and vitamins.

16. An anthelmintic composition of

about 0.08% ivermectin,

about 3% levamisole, and

about 2% albendazole

where different liquid carrier phases substantially partition the ivermectin from the levamisole, and

where the albendazole is particulate and is at least in part in an aqueous phase with the levamisole, such aqueous phase being buffered to a pH appropriate for the levamisole and its stability.

17. **A storage stable pourable pesticidal composition** having an organic first liquid phase and another ("second") liquid phase, said first phase including at least one active ingredient ("first active ingredient") (and optionally a co-solvent for said active ingredient) and said second phase including a second active ingredient

wherein the presence of an emulsifying agent and/or anti-flocculants ensures stability of the two phases with the first phase with its first active ingredient as an emulsion within said second phase with its second active ingredient.

18. **A stable mix of two or more immiscible liquids or liquid phases** held together by an emulsifier or emulsifiers where one phase is an organic water immiscible phase and another phase is an aqueous or organic phase.

19. A mix of claim 18 wherein said organic phase includes lactic acid.

20. **A benzimidazole composition** comprising an organic acid and a benzimidazole dissolved therein.

21. A composition of claim 20 wherein said organic acid is lactic acid.

22. **A topical or pour-on benzimidazole composition** where a benzimidazole is solubilised in an organic acid.

23. A composition of claim 22 wherein said organic acid is lactic acid.

24. **A benzimidazole containing composition** of at least two phases, where at least one phase is that of an organic acid which solubilises at least one benzimidazole active ingredient.

25. A composition of claim 24 wherein said organic acid is lactic acid.

26. **A ready to use pesticidal veterinary liquid composition** of at least a first active in a first liquid phase and at least a second active in a second liquid phase, the phases forming a stable emulsion.

27. **A storage stable pourable composition** comprising or including

up to 25% w/v of at least one pesticide (hereafter "first active(s)") soluble in an organic phase,

1 to 60% w/v of an organic phase (hereafter "first liquid phase") in which said first active(s) is (are) at least substantially soluble,

0 - 5% w/v of a co-solvent for said first active(s),

1 to 15% w/v of an emulsifying agent,

0 to 20% w/v of at least one further pesticidal active (hereafter "second active(s)") not substantially soluble in said first phase,

and,

a second liquid phase,

said composition having at least most of said first active(s) in said organic phase and said organic phase being emulsified in the second liquid phase which includes said second active(s).

28. A composition of claim 27 wherein said organic phase includes (i) a vegetable and/or mineral oil, (ii) at least one emollient ester, or (iii) both (i) and (ii).

29. **A storage stable composition** (whether as a concentrate for aqueous dilution or otherwise) comprising or including

up to 25% w/v of at least one pesticide (hereafter "first active(s)") chosen from the class of at least partly oil or emollient ester soluble actives,

1 to 60% w/v of at least one water immiscible organic phase in which said first active(s) is (are) at least substantially soluble,

0 - 5% w/v of a co-solvent for said first active(s),

1 to 15% w/v of an emulsifying agent,

0 to 20% w/v of at least one further pesticidal active (hereafter "second active(s)") not substantially soluble in said organic phase which is (i) dissolved in water and/or (ii) suspended in water,

and,

said water,

said composition having an organic phase with at least most of said first active(s), said organic phase being emulsified in an aqueous phase of said water and said second active(s).

30. **A storage stable pesticidal composition** having

an organic phase and an aqueous phase, said organic phase being of an oil and/or emollient ester which includes at least one active ingredient (and, optionally, a co-solvent for said active ingredient) and

an aqueous phase including a second active ingredient which is substantially insoluble in said organic phase

wherein at least one emulsifying agent and/or at least one anti-flocculant assists or ensures stability of the two phases with the organic phase as an emulsion within said aqueous phase.

31. **A pourable pesticidal composition** comprising or including

at least one active ingredient chosen from the class of macro cyclic lactones (hereafter "ML"),

at least one active ingredient chosen from the tetramisole/levamisole class,

at least one organic liquid carrier to provide a first liquid phase, and

means providing a second liquid phase,

and, optionally, an emulsifying agent or agents,

wherein said ML active ingredient(s) is(are) at least primarily in the first phase in solution,

and wherein said tetramisole/levamisole class active ingredient(s) is(are) at least primarily in solution in the second phase,

and wherein said phases exist in, or can be shaken or agitated into, the form of an emulsion.

32. A composition of claim 31 wherein said at least one organic liquid carrier is (i) at least

one oil or (ii) at least one oil and at least one organic co-solvent.

33. **A pesticidal composition** (whether as a concentrate for aqueous dilution or otherwise) comprising or including

at least one active ingredient chosen from the class of macro cyclic lactones (hereafter "ML"),

at least one active ingredient chosen from the tetramisole/levamisole class,

at least one organic liquid carrier, and

water,

and, optionally, an emulsifying agent or agents,

wherein said ML active ingredient(s) is(are) at least primarily in the organic liquid carrier(s) in solution (hereafter referred to as "the organic phase"),

and wherein said tetramisole/levamisole class active ingredient(s) is(are) at least primarily in solution in the water (hereafter referred to as "the aqueous phase"),

and wherein said organic phase and said aqueous phase exist in, or can be shaken or agitated into, the form of an emulsion.

34. A composition of claim 33 wherein said at least one organic liquid carrier is (i) at least one oil or (ii) at least one oil and at least one organic co-solvent

35. **A stable pourable composition** comprising or including

at least one anthelmintic active (hereafter "first anthelmintic active(s)"),

at least one liquid to provide a first phase in which said first anthelmintic active(s) is (are) at least substantially soluble,

an emulsifying agent,

at least one liquid to provide a second phase, and

at least one further anthelmintic active (hereafter "second anthelmintic active(s)") not substantially soluble in said first phase,

said composition having a first phase with at least most of said first anthelmintic active(s) and a second phase of at least most of said second anthelmintic active(s).

36. **A stable composition** (whether as a concentrate for aqueous dilution or otherwise) comprising or including

at least one anthelmintic (hereafter "first anthelmintic active(s)") chosen from the class of at least partly oil soluble anthelmintic actives,

at least one oil (optionally also with an organic co-solvent) in which said first anthelmintic active(s) is (are) at least substantially soluble,

an emulsifying agent,

water, and

at least one further anthelmintic active (hereafter "second anthelmintic active(s)") not substantially soluble in said oil(s) which is (i) dissolved in said water and/or (ii) suspended in said water,

said composition having an organic phase of said oil(s) with at least most of said first anthelmintic active(s) and an aqueous phase of said water and at least most of said second anthelmintic active(s).

37. **A stable formulation** of

a first active in an organic ("first") phase,

a second active in a second liquid phase, and

additional actives in one or other, or both, said phase(s),

and wherein said phases provide a stable emulsion,

and wherein at least one of said first and second actives is an anthelmintic active.

38. **A stable formulation** of

a first active in an organic phase at least primarily of oil(s),

a second active in an aqueous phase, and

additional actives in one or other, or both, said organic and aqueous phase(s),

and wherein said organic and aqueous phases provide a stable emulsion,

and wherein at least one of said first and second actives is an anthelmintic active.

39. **A pesticidal composition comprising** or including

(i) at least one active ingredient chosen from the class of macro cyclic lactones

(hereafter "ML"),

(ii) at least one organic liquid carrier which carries at least most of said ML active ingredient(s), thereby defining an organic liquid phase,

(iii) levamisole, and

(iv) at least water which carries at least most of said levamisole thereby defining

an aqueous phase,

wherein said aqueous phase has and/or is buffered to a pH of less than 7,

and wherein there is present in said aqueous phase either or both

(a) an emulsifying agent or agents, and

(b) a particulate content,

and wherein said phases exist in, or can be shaken or agitated into, the form of an emulsion with said particulate content, if any, at least substantially present in the aqueous phase.

40. **An anthelmintic oil in water emulsion carrying** at least one macro cyclic lactone (ML) in the oil phase and particles of levamisole and an emulsifying agent for the levamisole in the aqueous phase.

41. **A method of formulating an anthelmintic composition** of a kind having

at least one anthelmintic (hereafter "first active(s)"),

a liquid or liquids to define a first phase in which said first active(s) is (are) at least substantially soluble,

(optionally) an emulsifying agent,

at least one further anthelmintic active (hereafter "second active(s)") not substantially soluble in said first phase

(optionally) anti-flocculant(s),

and,

a liquid or liquids to define a second phase,

said method comprising or including the steps of

(I)(a) providing a mix of said first active ingredient and at least the first phase liquid(s),

(b) providing a mix of said second active ingredient and at least the second phase liquid(s), and

(II) by mixing at least the mixes of (I)(a) and (I)(b) forming an emulsion with at least most of said first active in the first phase and at least most of the second active in the second phase.

42. **A method of formulating an anthelmintic composition** of a kind having

at least one anthelmintic (hereafter "first active(s)") chosen from the class of (at least partly) oil soluble anthelmintic actives,

an oil or oils in which said first active(s) is (are) at least substantially soluble,

optionally a co-solvent for said first active(s),

an emulsifying agent,

at least one further anthelmintic active (hereafter "second active(s)") not substantially soluble in said oil(s),

optional anti-flocculant(s),

and,

water,

said method comprising or including the steps of

(I)(a) providing a mix of said first active ingredient, the oil(s), the optional co-solvent(s) and the emulsifying agent(s),

(b) providing a mix of said second active ingredient the water, and the optional anti-flocculant(s), and

(II) by mixing at least the mixes of (I)(a) and (I)(b) forming an emulsion with at least most of said first active in the oil(s) and at least most of the second active in the aqueous phase.

43. **An anthelmintic composition** made by a method of claim 41 or 42.

44. **A method of treating mammals for pests** which involves (whether with dilution or not) administering or having self administered to such mammals effective amounts of active(s) of compositions of any one of claims 1 to 17, 20 to 40 and 43.

45. **The use of an anthelmintic composition** of any of the kinds defined in any one of claims 1 to 17, 20 to 40 and 43.

46. **A partitioned biocidal composition** comprising in an organic phase a first biocide,

and in an aqueous phase at acid pH a second biocide, said first biocide being unstable chemically at said acid pH.

47. A partitioned biocidal composition as claimed in claim 46 having particles suspended in at least the aqueous phase.

48. A partitioned biocidal composition as claimed in claim 47 wherein said particles are

themselves biocidal.

49. A partitioned biocidal composition as claimed in claim 47 wherein said particles are of

a benzimidazole anthelmintic.

50. A partitioned biocidal composition of claim 47, 48 or 49 wherein said particles are

substantially all less than 20μ.

51. A partitioned veterinary biocidal composition of any one of claims 46 to 50.

52. A partitioned composition of any one of claims 46 to 51 which is also a composition of

any one of claims 1 to 17, 20 to 40 and 43.

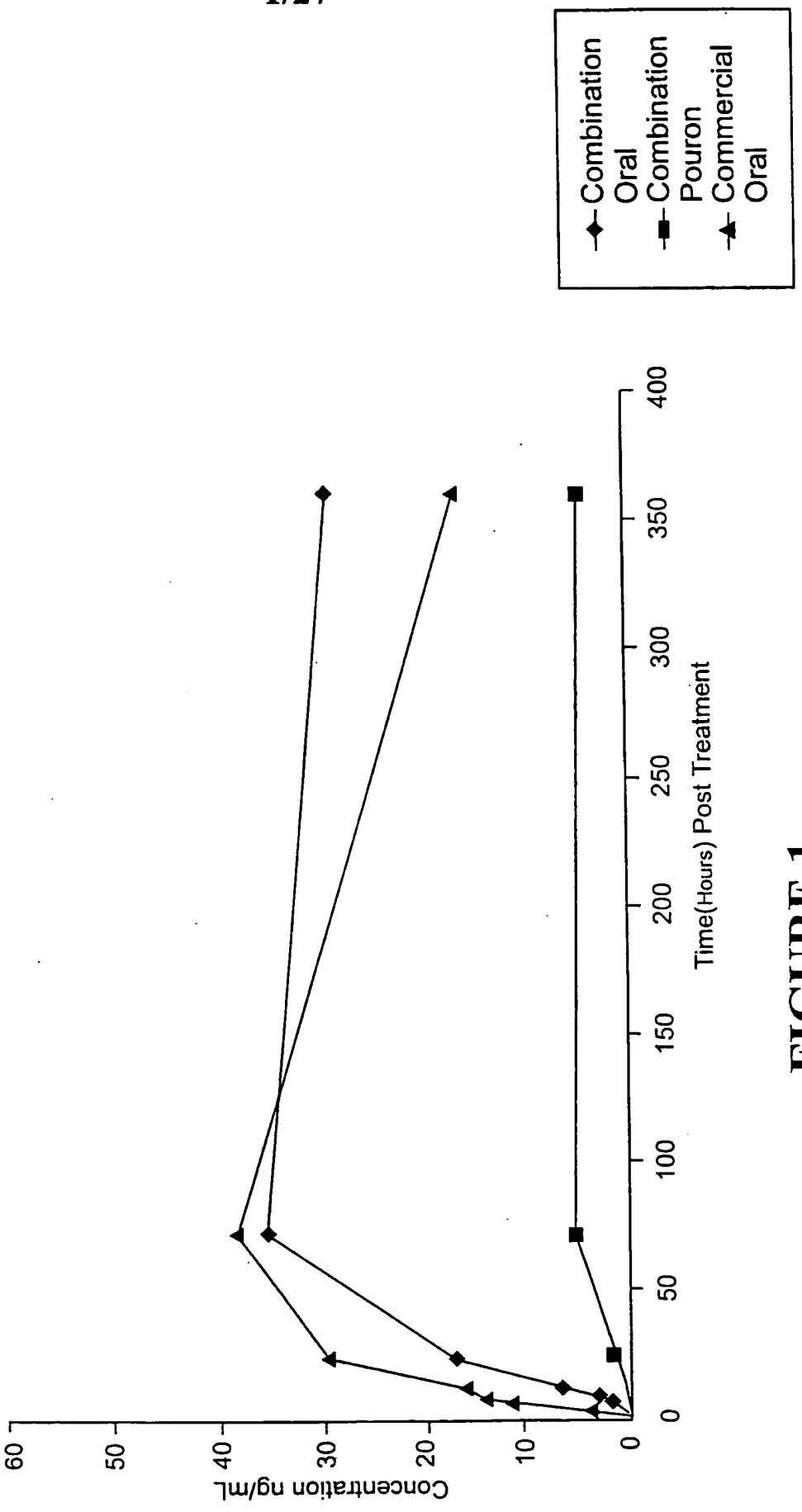

ABAMECTIN (AVERMECTIN B1a)
Cattle: Mean Blood Levels
Trial NCOO1
Combination Oral
Combination Pouron
Commercial Oral
Concentration ng/mL
Time(Hours) Post Treatment
0
10
20
30
40
50
60
0
50
100
150
200
250
300
350
400

FIGURE 1

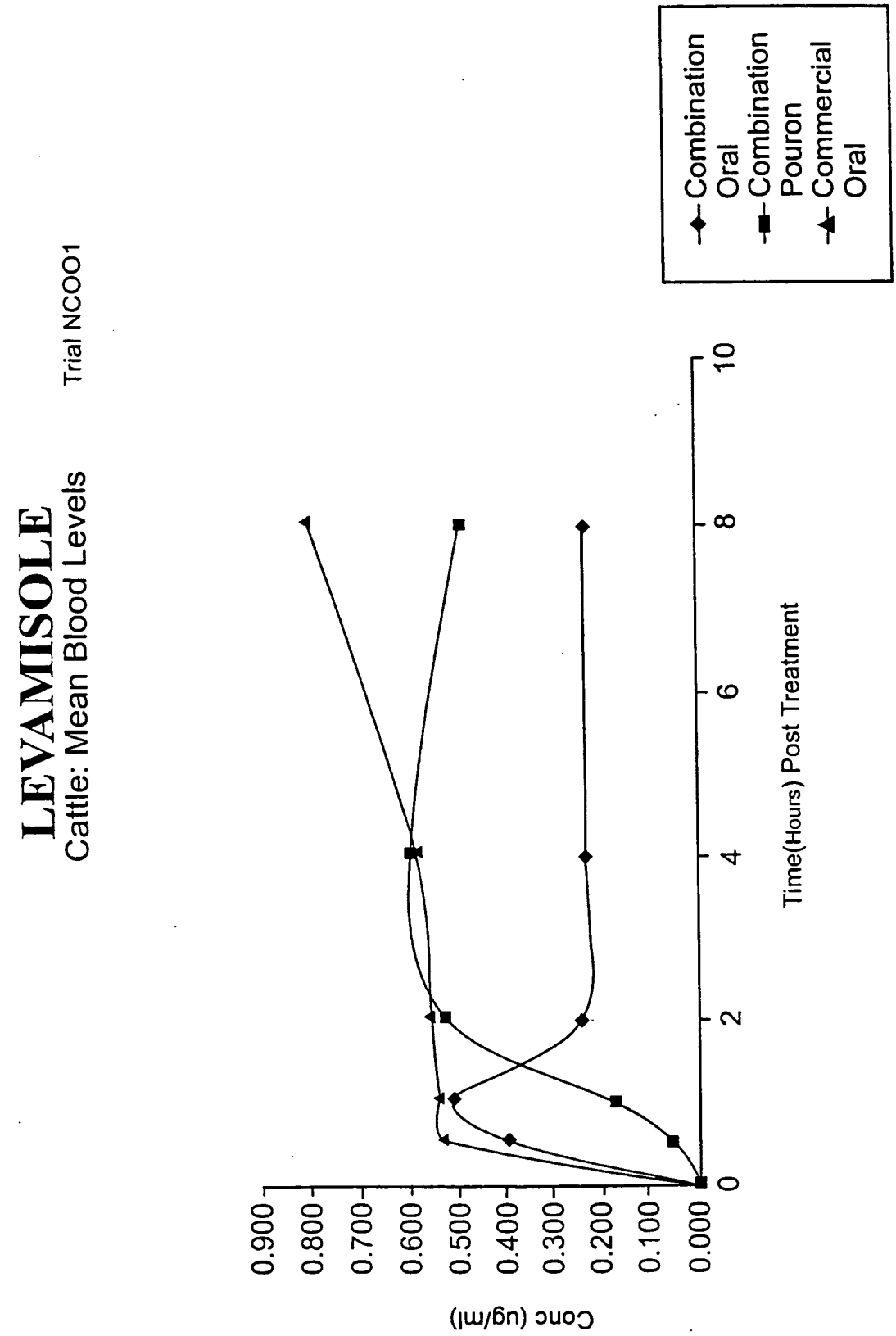

LEVAMISOLE
Cattle: Mean Blood Levels
Trial NCOO1
Combination Oral
Combination Pouron
Commercial Oral
Conc (ug/ml)
0.900
0.800
0.700
0.600
0.500
0.400
0.300
0.200
0.100
0.000
0
2
4
6
8
10
Time(Hours) Post Treatment

FIGURE 2

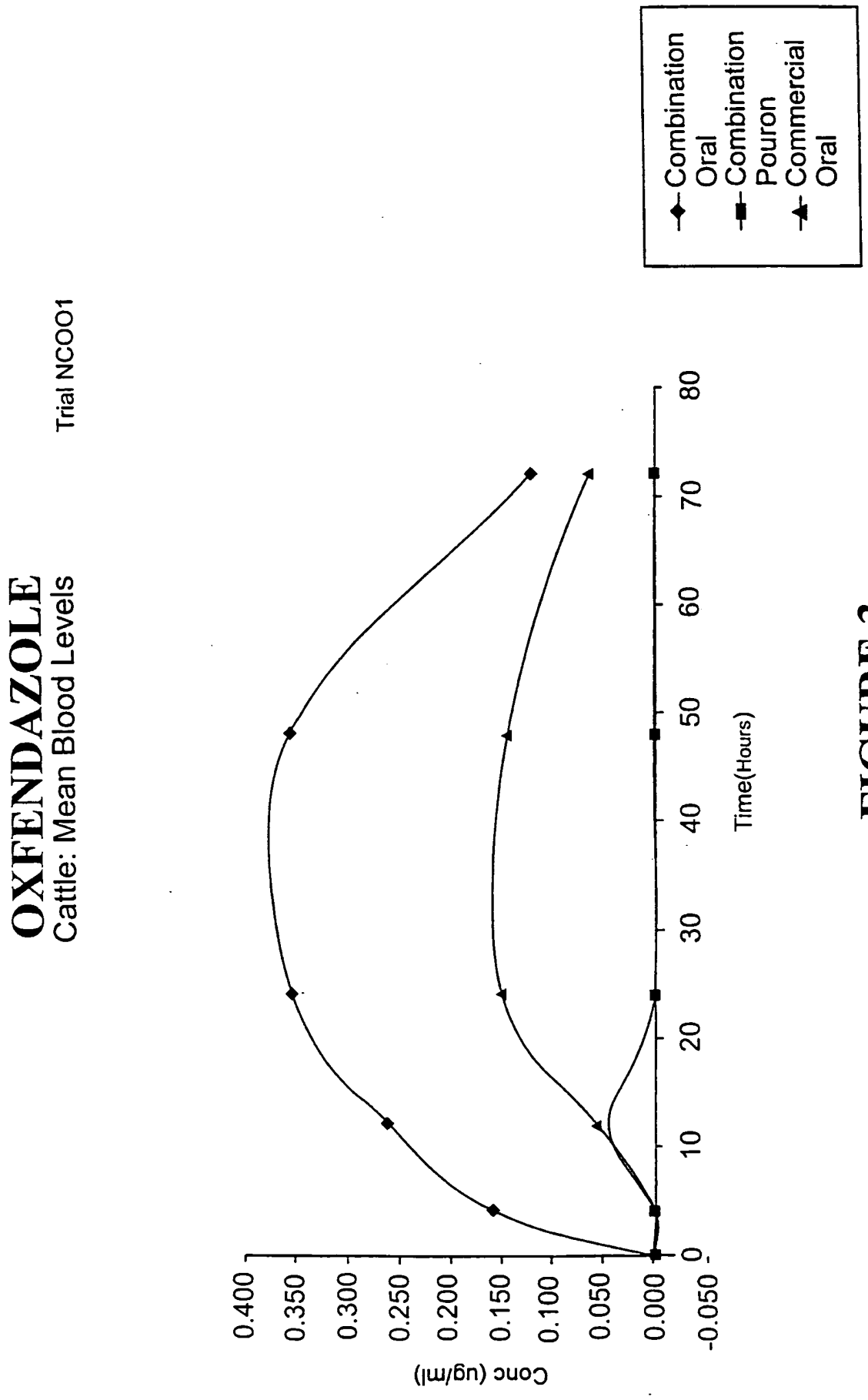

OXFENDAZOLE
Cattle: Mean Blood Levels
Trial NC001
Combination Oral
Combination Pouron
Commercial Oral
Conc (ug/ml)
0.400
0.350
0.300
0.250
0.200
0.150
0.100
0.050
0.000
-0.050
0
10
20
30
40
50
60
70
80
Time(Hours)

FIGURE 3

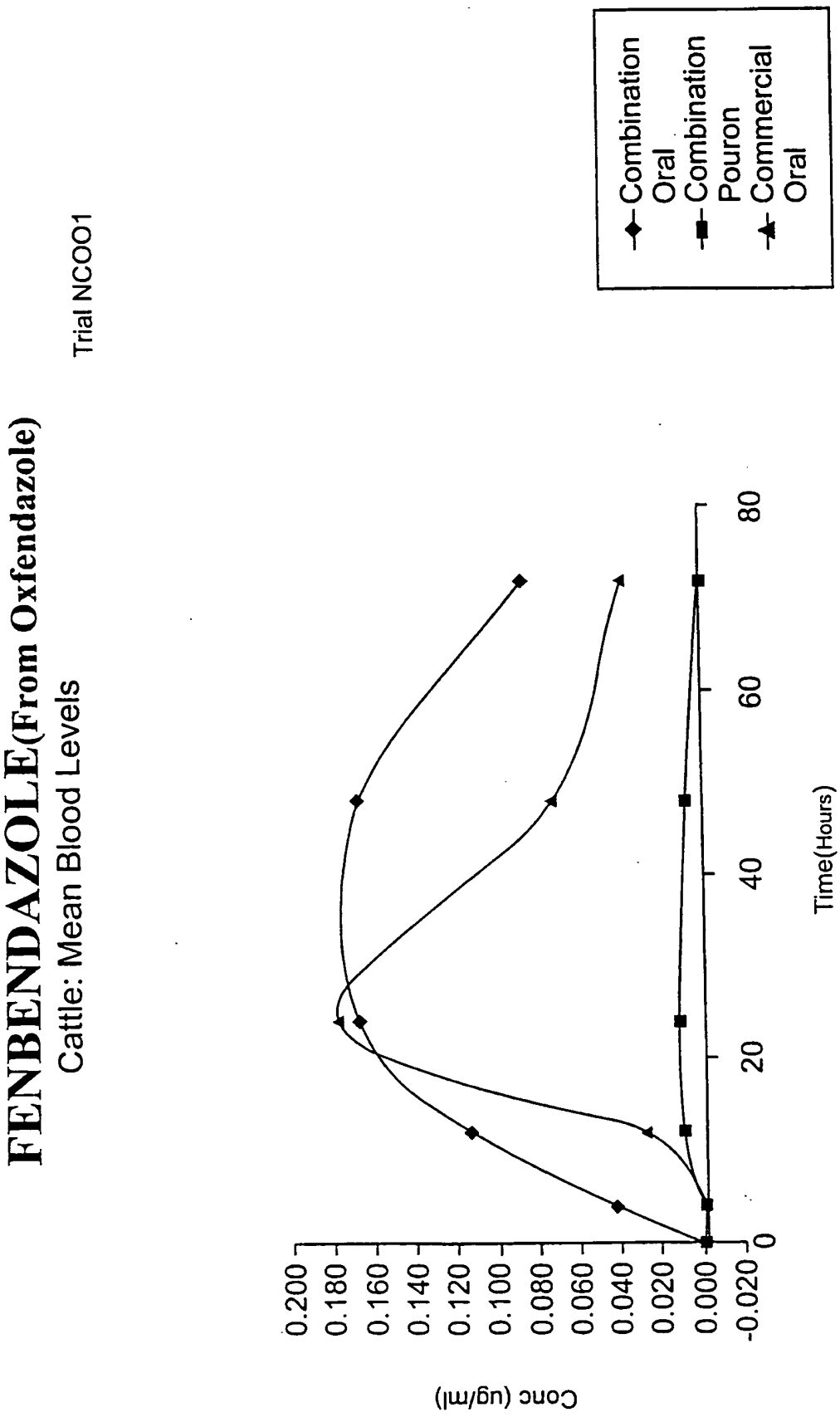

FENBENDAZOLE(From Oxfendazole)
Cattle: Mean Blood Levels
Trial NCOO1
Combination Oral
Combination Pouron
Commercial Oral
Conc (ug/ml)
0.200
0.180
0.160
0.140
0.120
0.100
0.080
0.060
0.040
0.020
0.000
-0.020
0
20
40
60
80
Time(Hours)

FIGURE 4

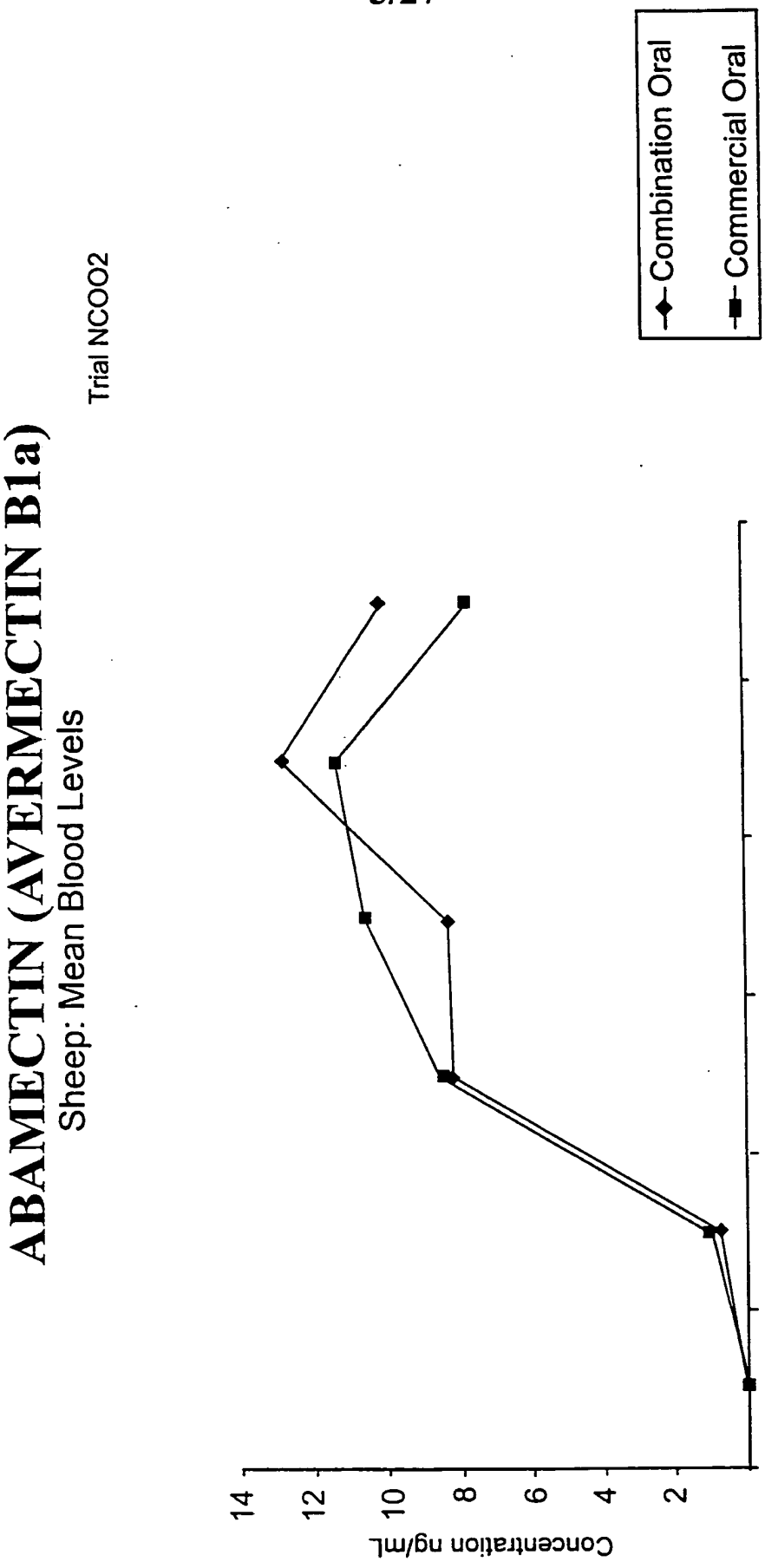

ABAMECTIN (AVERMECTIN B1a)
Sheep: Mean Blood Levels
Trial NCOO2
Combination Oral
Commercial Oral
Concentration ng/mL
Time(Hours)
0
2
8
12
24
48
2
4
6
8
10
12
14

FIGURE 5

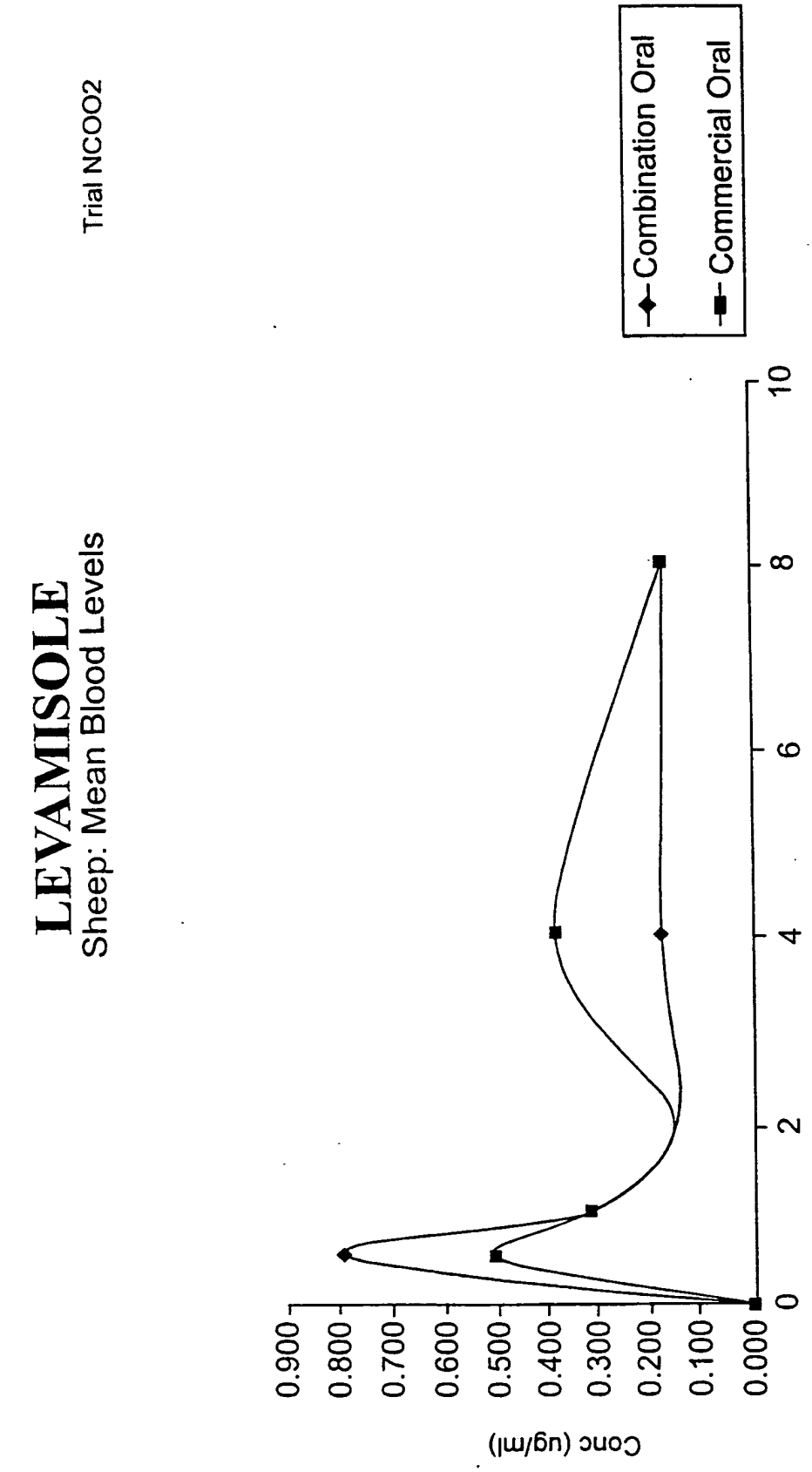

LEVAMISOLE
Sheep: Mean Blood Levels
Trial NCOO2
Combination Oral
Commercial Oral
Conc (ug/ml)
0.900
0.800
0.700
0.600
0.500
0.400
0.300
0.200
0.100
0.000
0
2
4
6
8
10
Time(Hours)

FIGURE 6

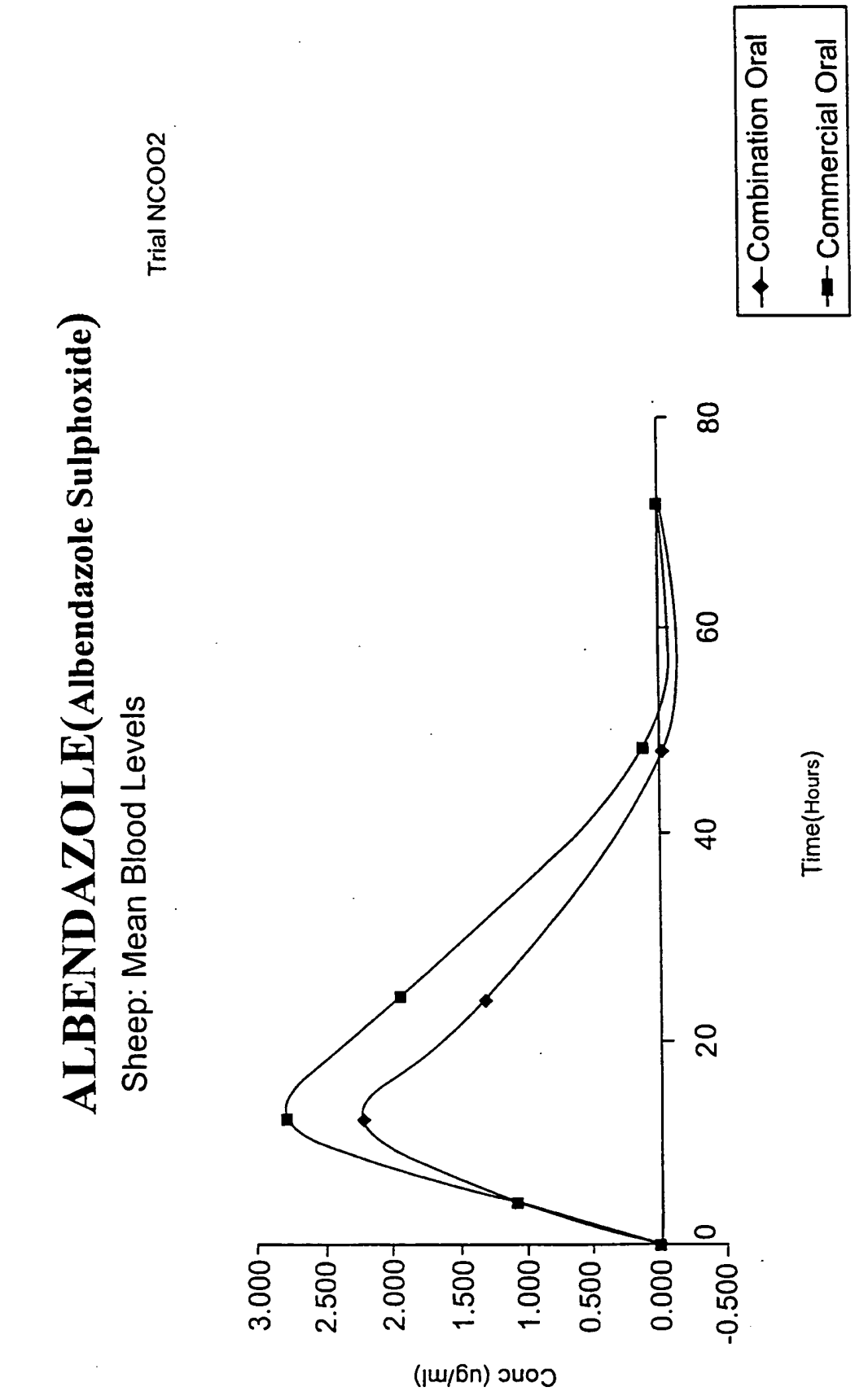

ALBENDAZOLE(Albendazole Sulphoxide)
Sheep: Mean Blood Levels
Trial NCOO2
Combination Oral
Commercial Oral
Conc (ug/ml)
3.000
2.500
2.000
1.500
1.000
0.500
0.000
-0.500
0
20
40
60
80
Time(Hours)

FIGURE 7

FIGURE 8

LB98/92 Abamectin Stability with Time

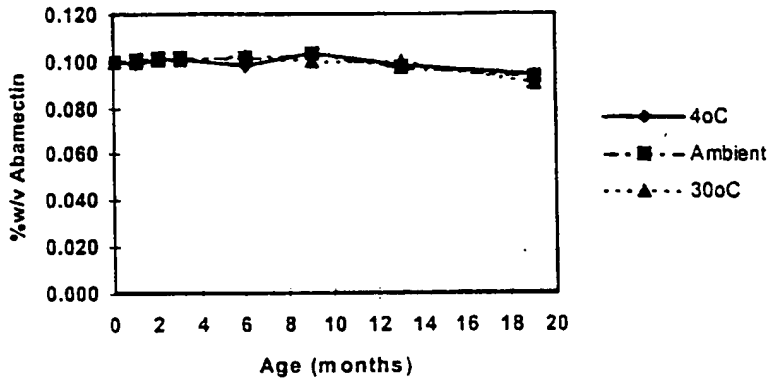


FIGURE 9

LB98/92 Levamisole Stability with Time

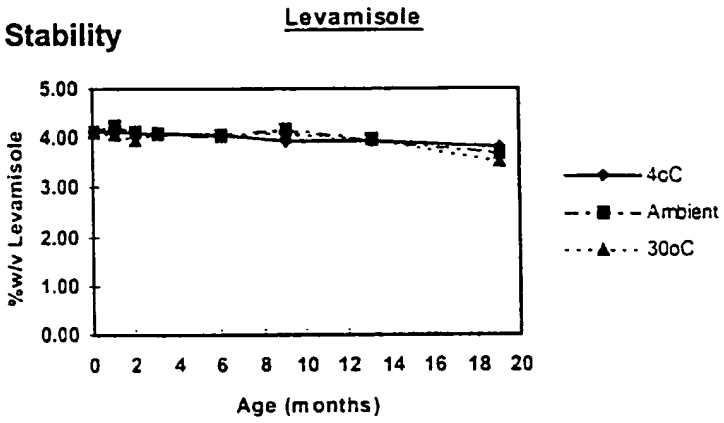
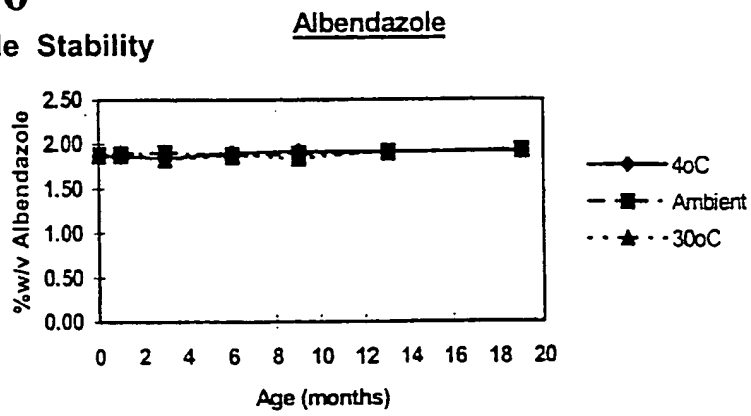


FIGURE 10

LB98/92 Albendazole Stability with Time



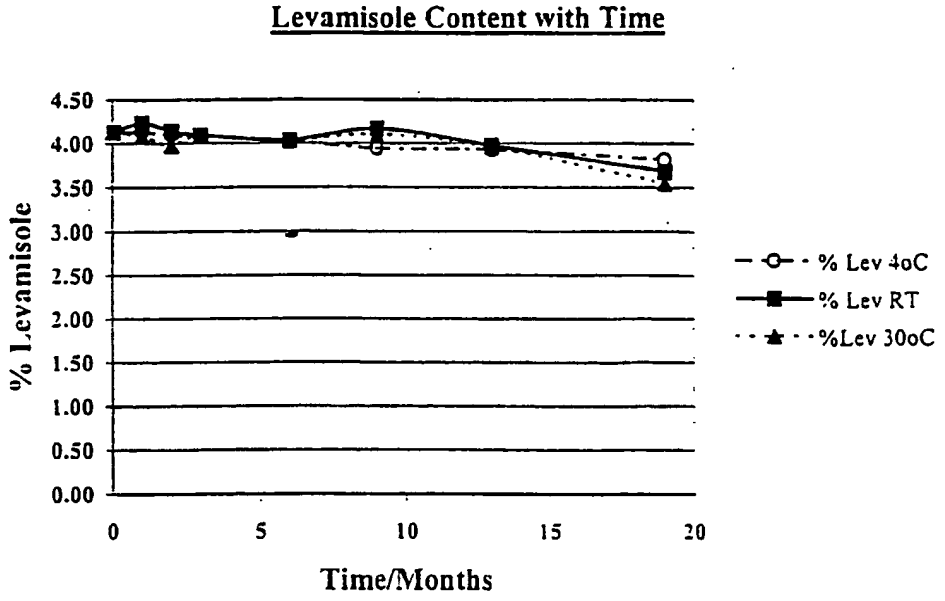


FIGURE 11 LB98/92

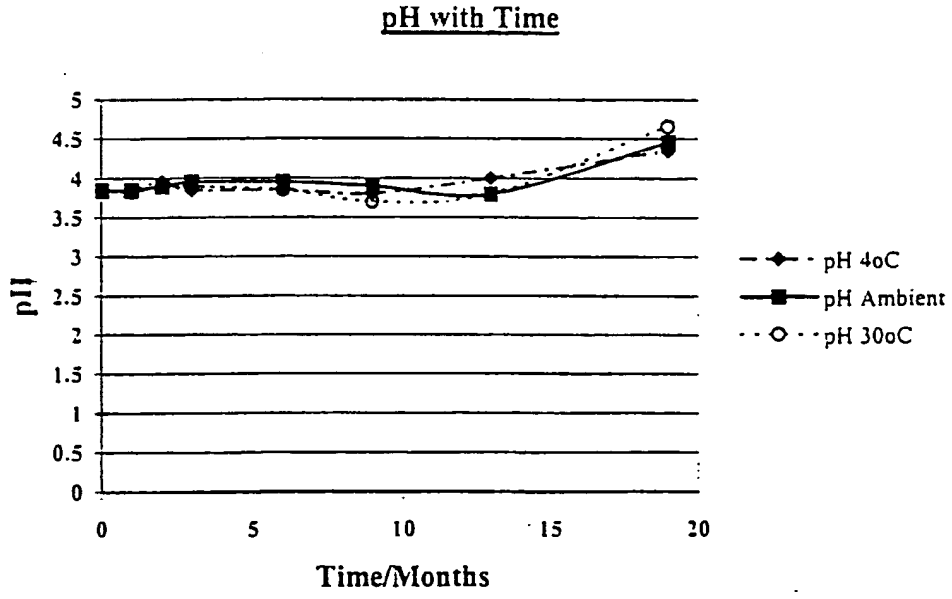


FIGURE 12 LB98/92

Stability graph for LB99/01

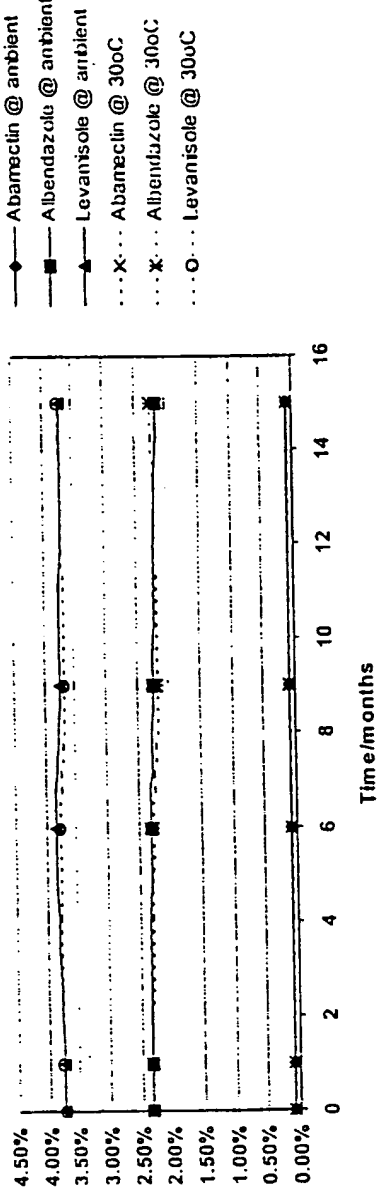


FIGURE 13

Stability graph of LB99/2

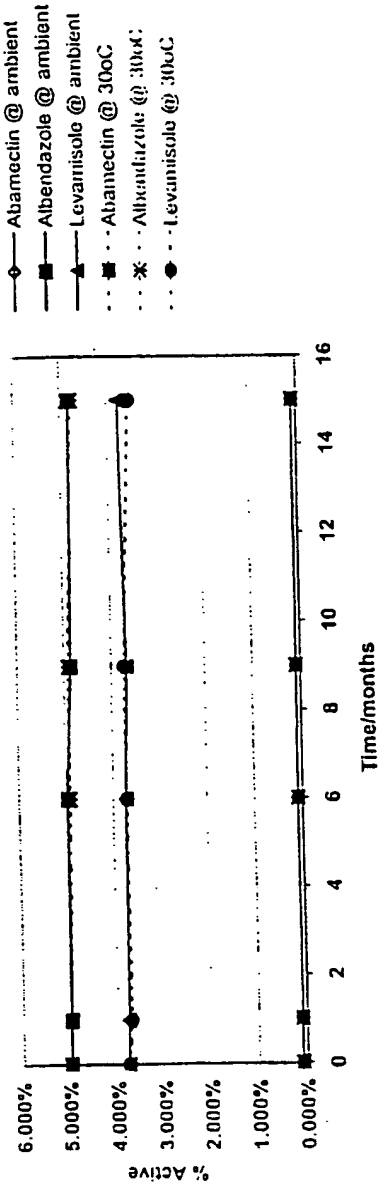


FIGURE 14

Stability Graph of LB99/03

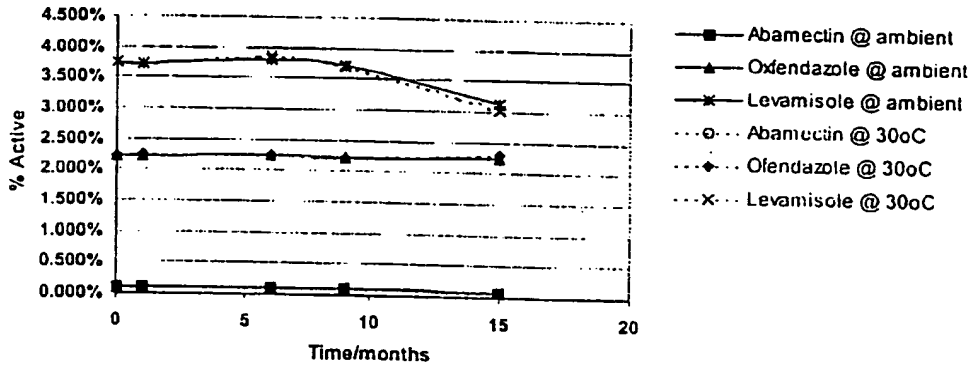


FIGURE 15

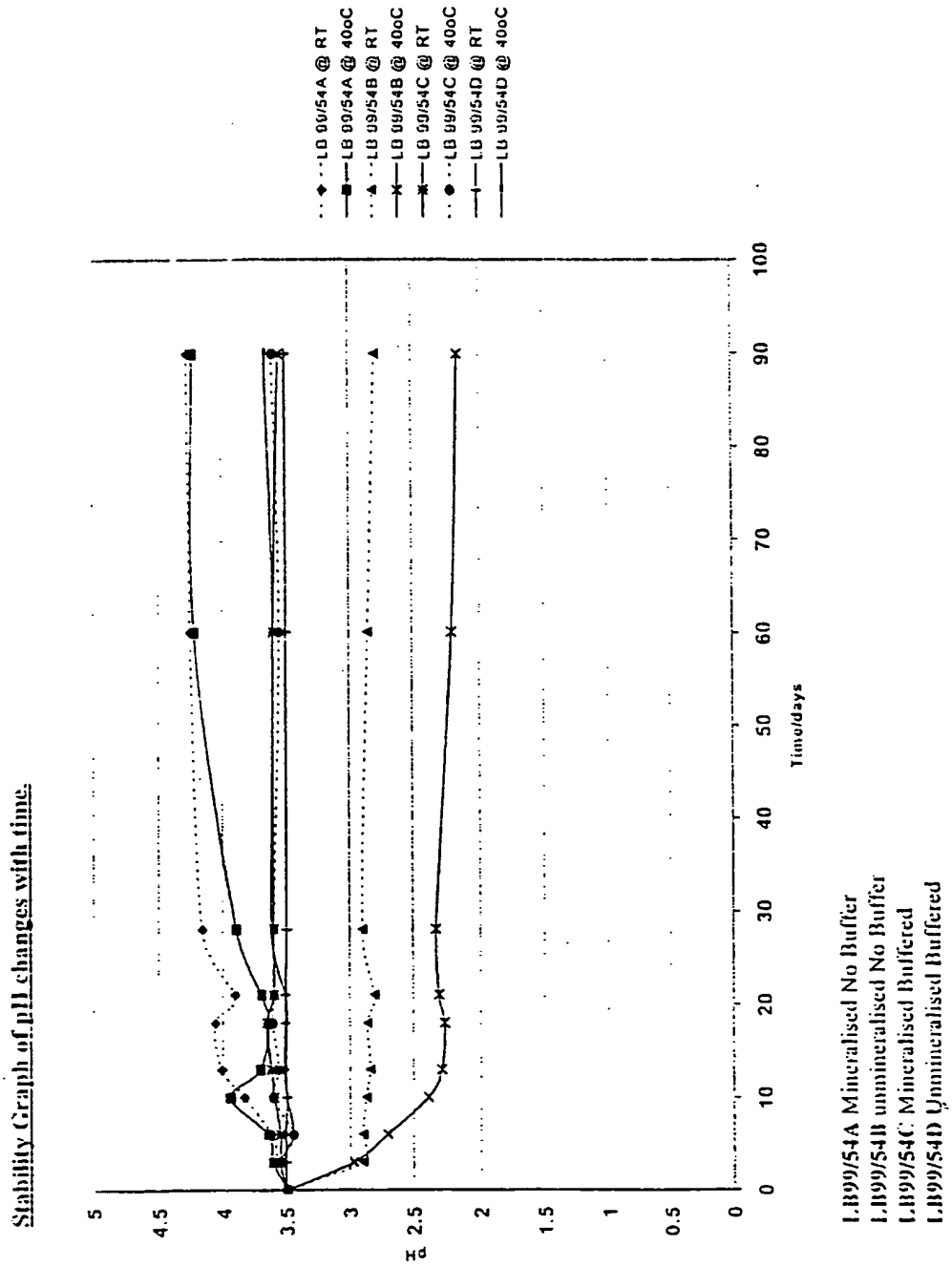

Stability Graph of pH changes with time.
LD 99/54A @ RT
LB 99/54A @ 40oC
LB 99/54B @ RT
LB 99/54B @ 40oC
LB 99/54C @ RT
LB 99/54C @ 40oC
LB 99/54D @ RT
LB 99/54D @ 40oC
pH
Time/days
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
0
10
20
30
40
50
60
70
80
90
100
LB99/54A Mineralised No Buffer
LB99/54B unmineralised No Buffer
LB99/54C Mineralised Buffered
LB99/54D Unmineralised Buffered

FIGURE 16

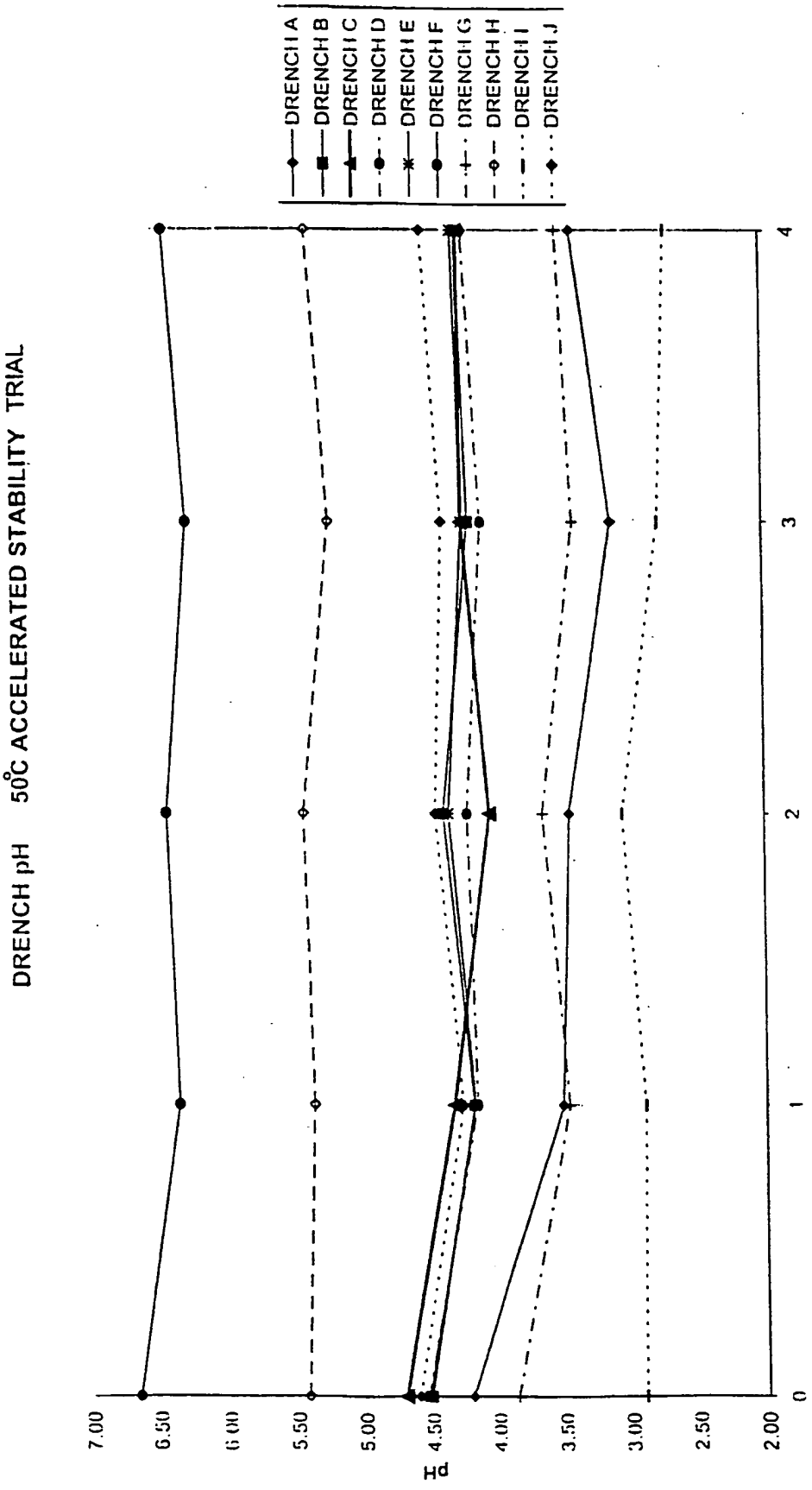

DRENCH pH 50°C ACCELERATED STABILITY TRIAL
DRENCH A
DRENCH B
DRENCH C
DRENCH D
DRENCH E
DRENCH F
DRENCH G
DRENCH H
DRENCH I
DRENCH J
pH
7.00
6.50
6.00
5.50
5.00
4.50
4.00
3.50
3.00
2.50
2.00
0
1
2
3
4
WEEKS

FIGURE 17

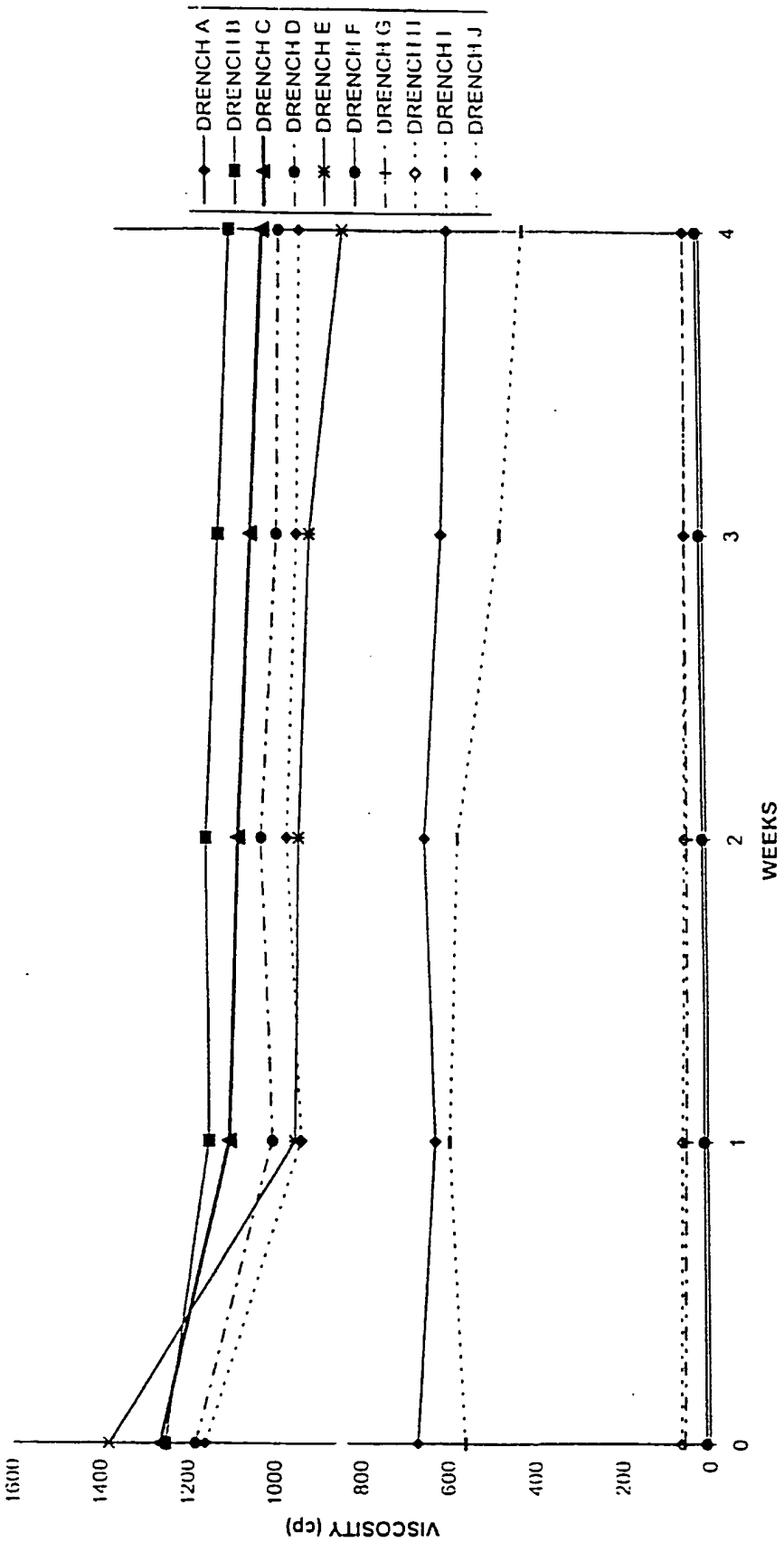

DRENCH VISCOSITY 50°C ACCELERATED STABILITY TRIAL
DRENCH A
DRENCH B
DRENCH C
DRENCH D
DRENCH E
DRENCH F
DRENCH G
DRENCH H
DRENCH I
DRENCH J
VISCOSITY (cp)
1600
1400
1200
1000
800
600
400
200
0
WEEKS
0
1
2
3
4

FIGURE 18

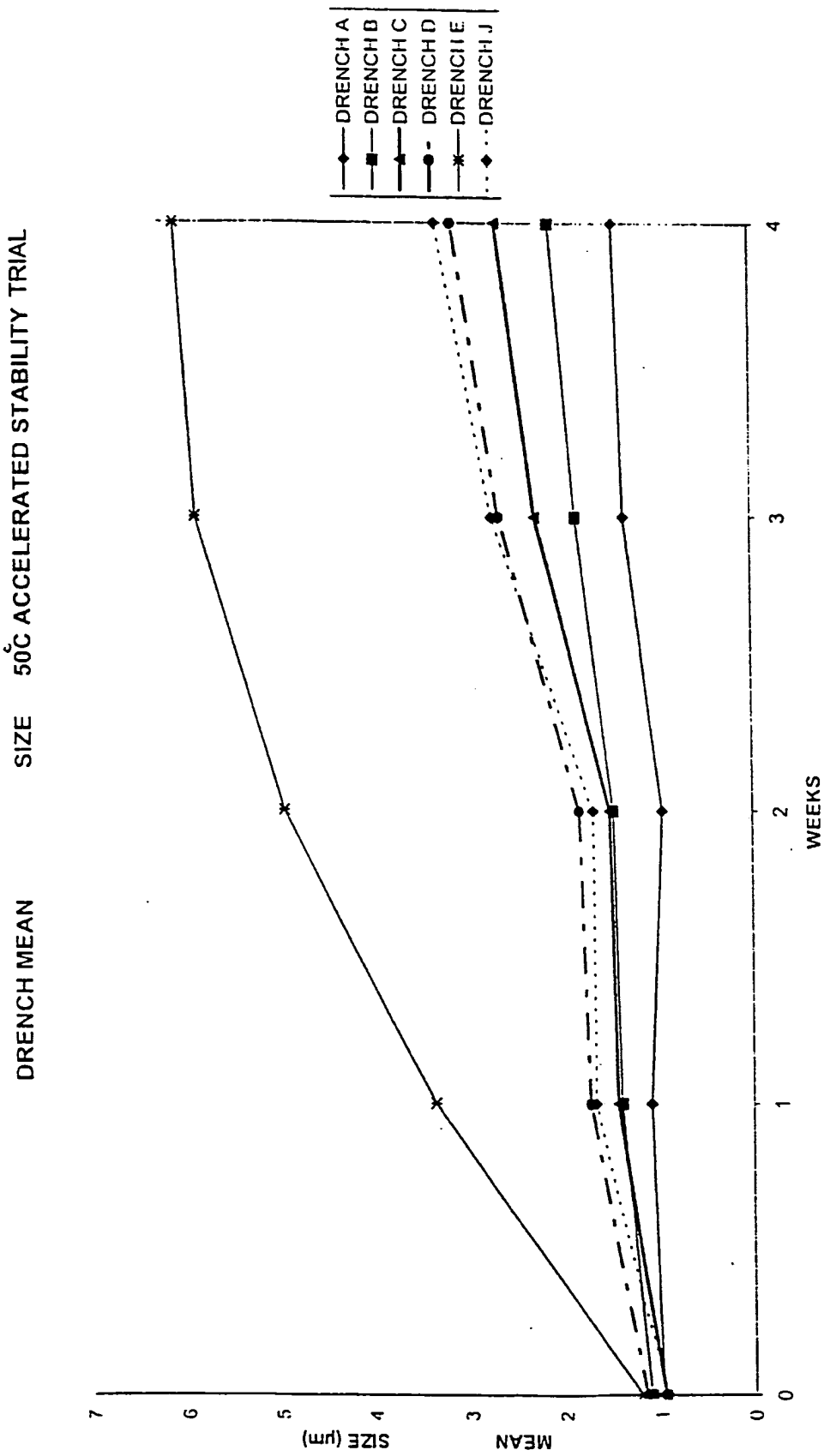

DRENCH MEAN SIZE 50C ACCELERATED STABILITY TRIAL
DRENCH A
DRENCH B
DRENCH C
DRENCH D
DRENCH E
DRENCH J
MEAN SIZE (µm)
0
1
2
3
4
5
6
7
WEEKS
0
1
2
3
4

FIGURE 19

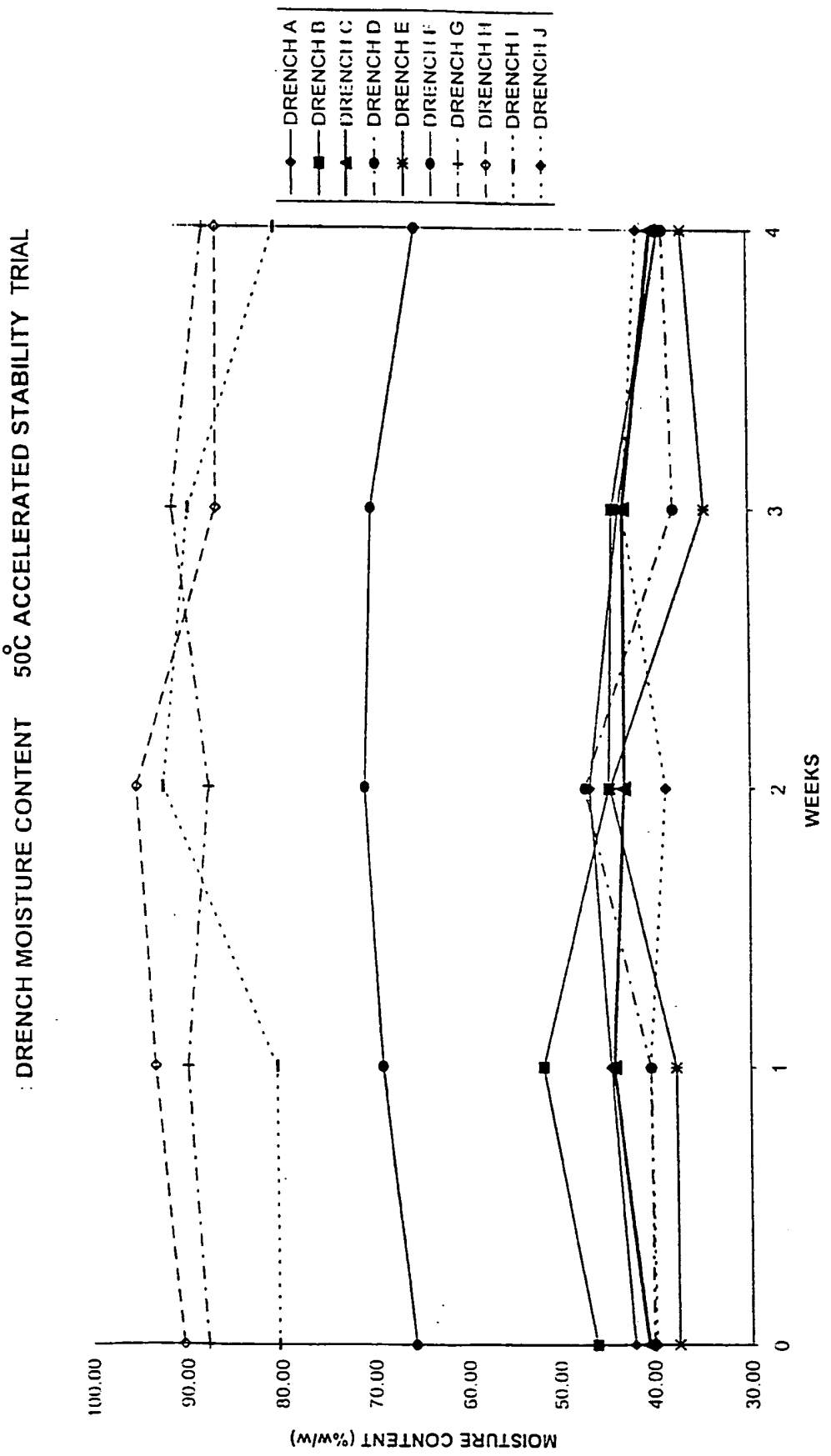

DRENCH MOISTURE CONTENT 50°C ACCELERATED STABILITY TRIAL
DRENCH A
DRENCH B
DRENCH C
DRENCH D
DRENCH E
DRENCH F
DRENCH G
DRENCH H
DRENCH I
DRENCH J
MOISTURE CONTENT (%w/w)
100.00
90.00
80.00
70.00
60.00
50.00
40.00
30.00
WEEKS
0
1
2
3
4

FIGURE 20

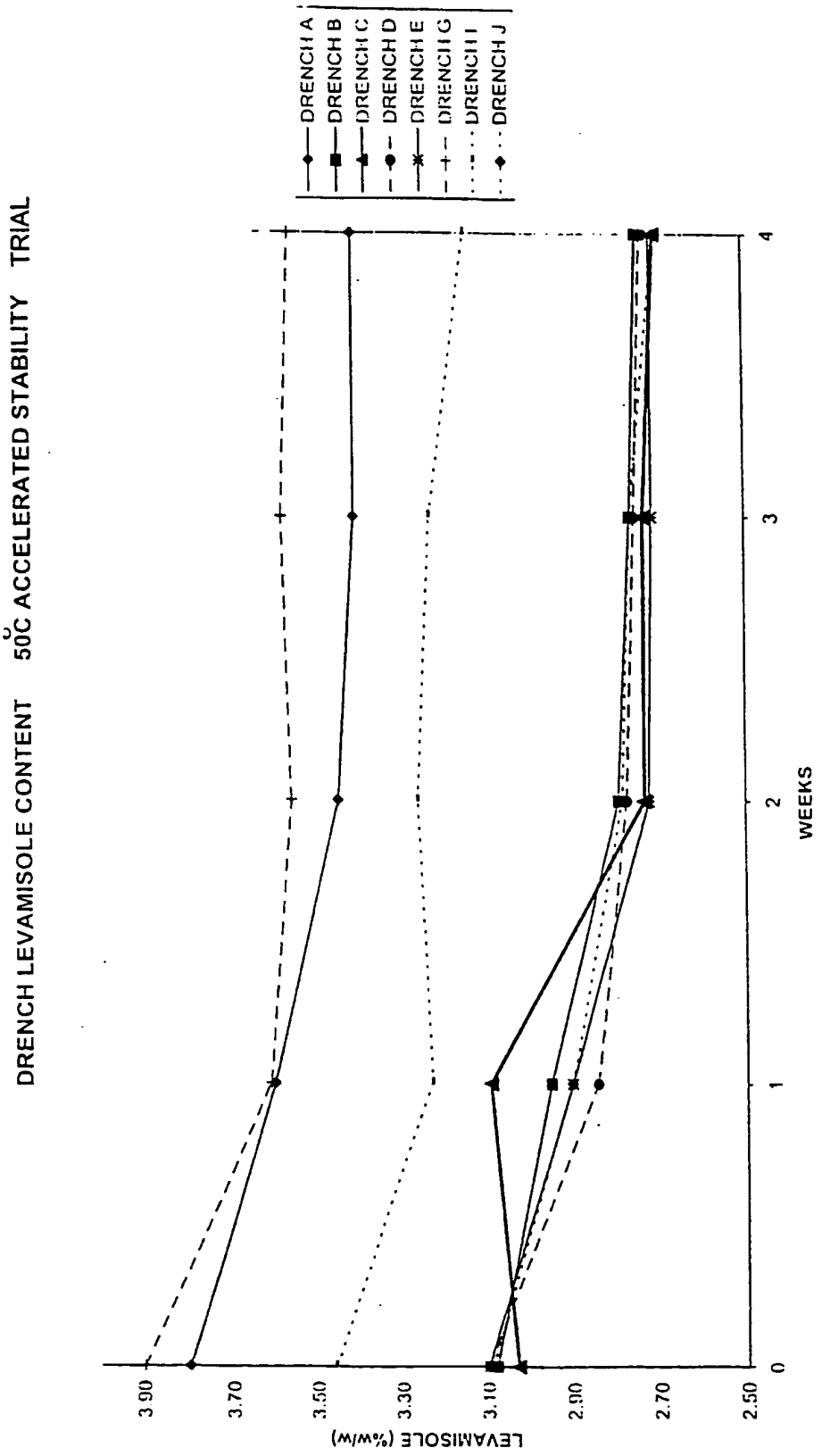

DRENCH LEVAMISOLE CONTENT 50C ACCELERATED STABILITY TRIAL
DRENCH A
DRENCH B
DRENCH C
DRENCH D
DRENCH E
DRENCH G
DRENCH I
DRENCH J
LEVAMISOLE (%w/w)
3.90
3.70
3.50
3.30
3.10
2.90
2.70
2.50
WEEKS
0
1
2
3
4

FIGURE 21

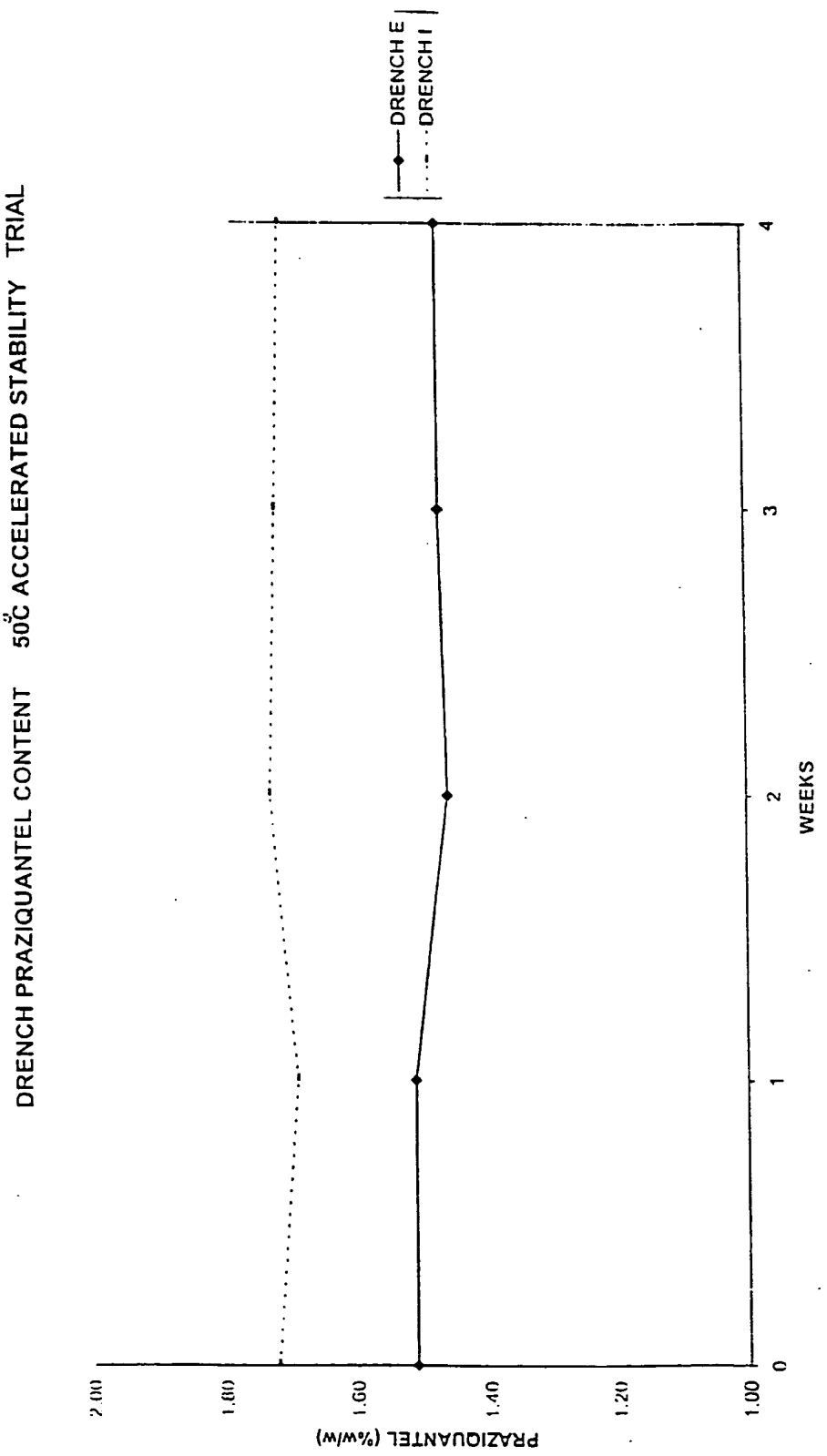

DRENCH PRAZIQUANTEL CONTENT 50°C ACCELERATED STABILITY TRIAL
DRENCH E
DRENCH I
PRAZIQUANTEL (%w/w)
2.00
1.80
1.60
1.40
1.20
1.00
0
1
2
3
4
WEEKS

FIGURE 22

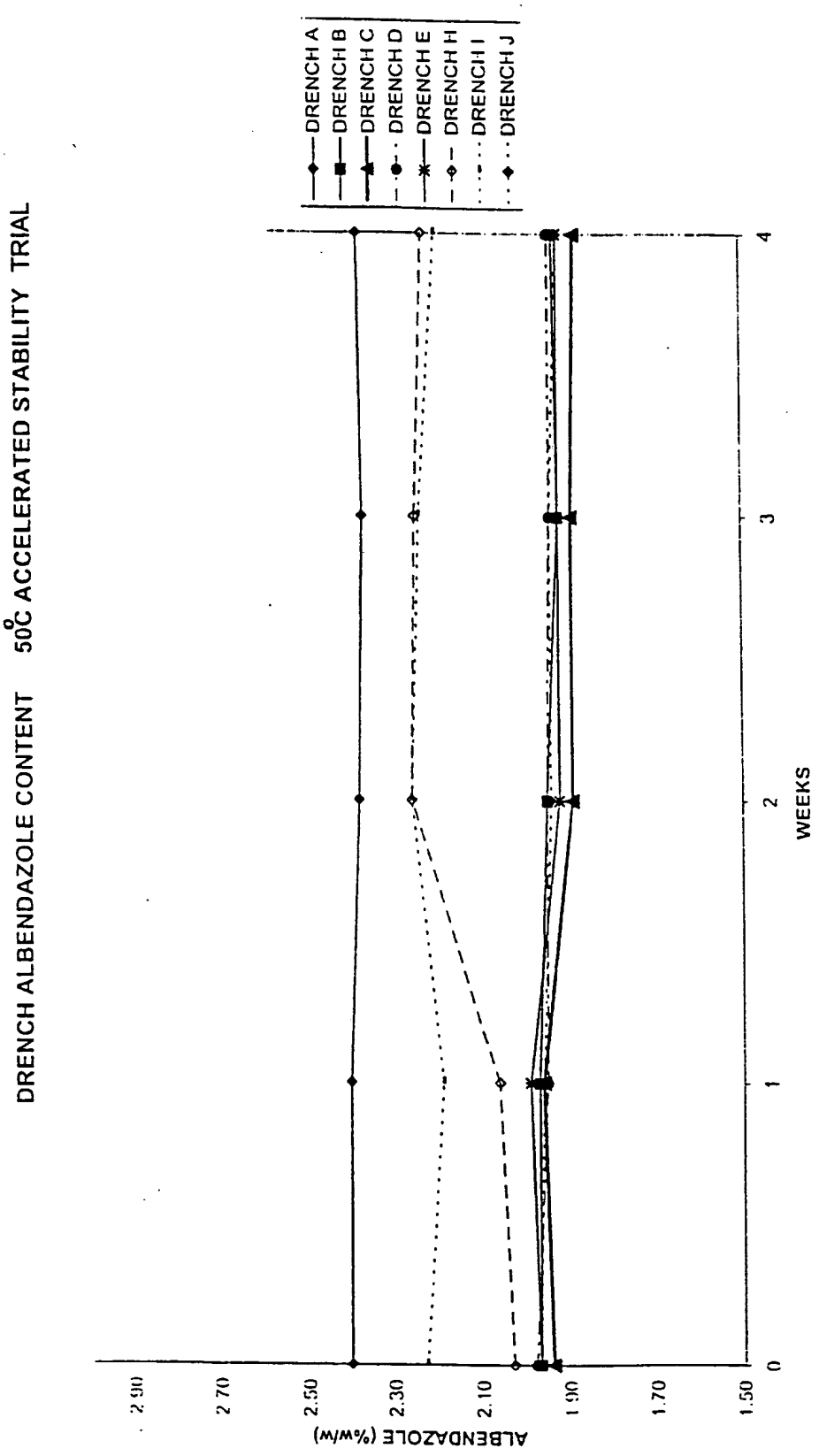

DRENCH ALBENDAZOLE CONTENT 50°C ACCELERATED STABILITY TRIAL
DRENCH A
DRENCH B
DRENCH C
DRENCH D
DRENCH E
DRENCH H
DRENCH I
DRENCH J
ALBENDAZOLE (%w/w)
2.90
2.70
2.50
2.30
2.10
1.90
1.70
1.50
0
1
2
3
4
WEEKS

FIGURE 23

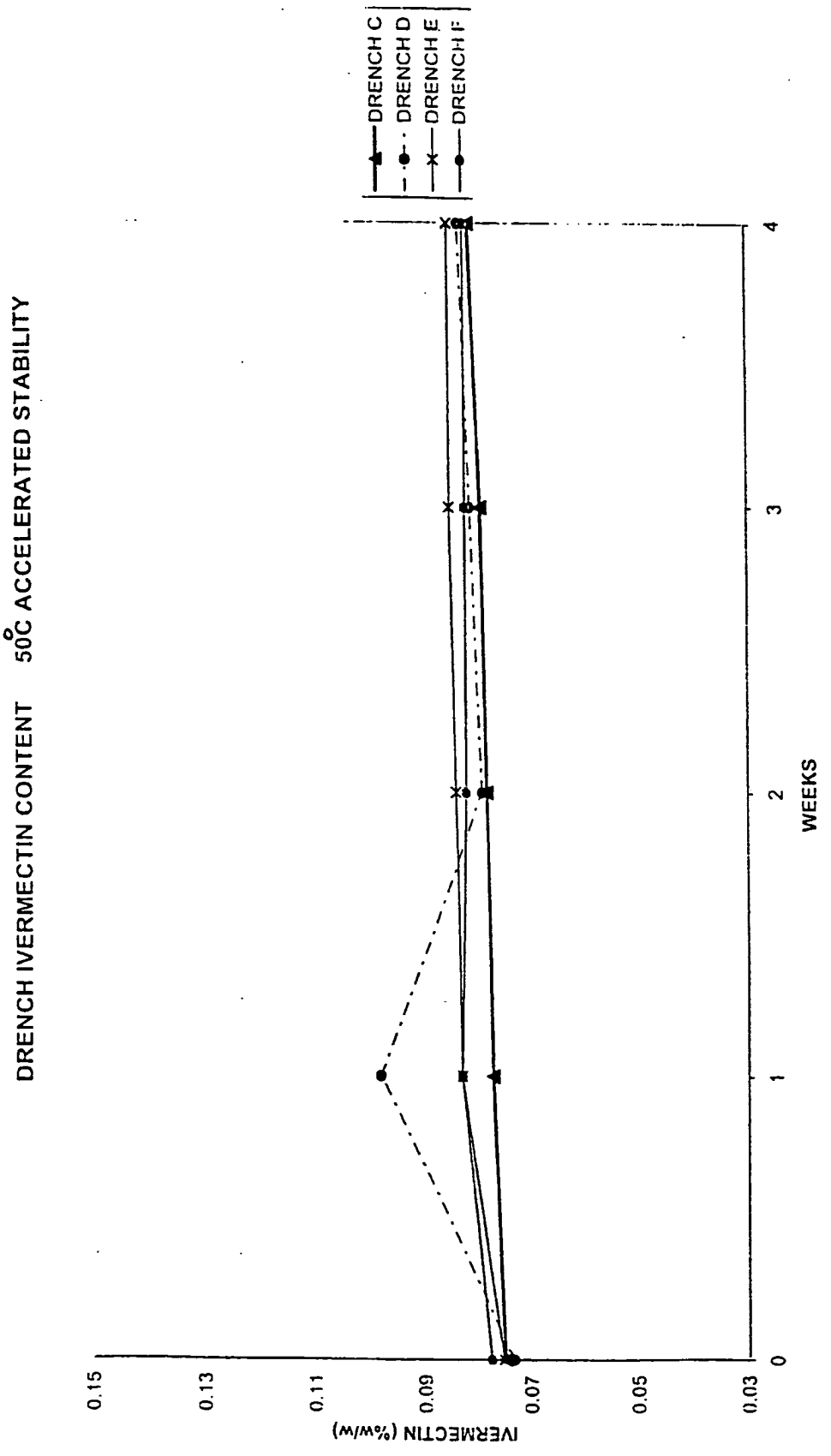

DRENCH IVERMECTIN CONTENT 50°C ACCELERATED STABILITY
DRENCH C
DRENCH D
DRENCH E
DRENCH F
IVERMECTIN (%w/w)
0.15
0.13
0.11
0.09
0.07
0.05
0.03
WEEKS
0
1
2
3
4

FIGURE 24

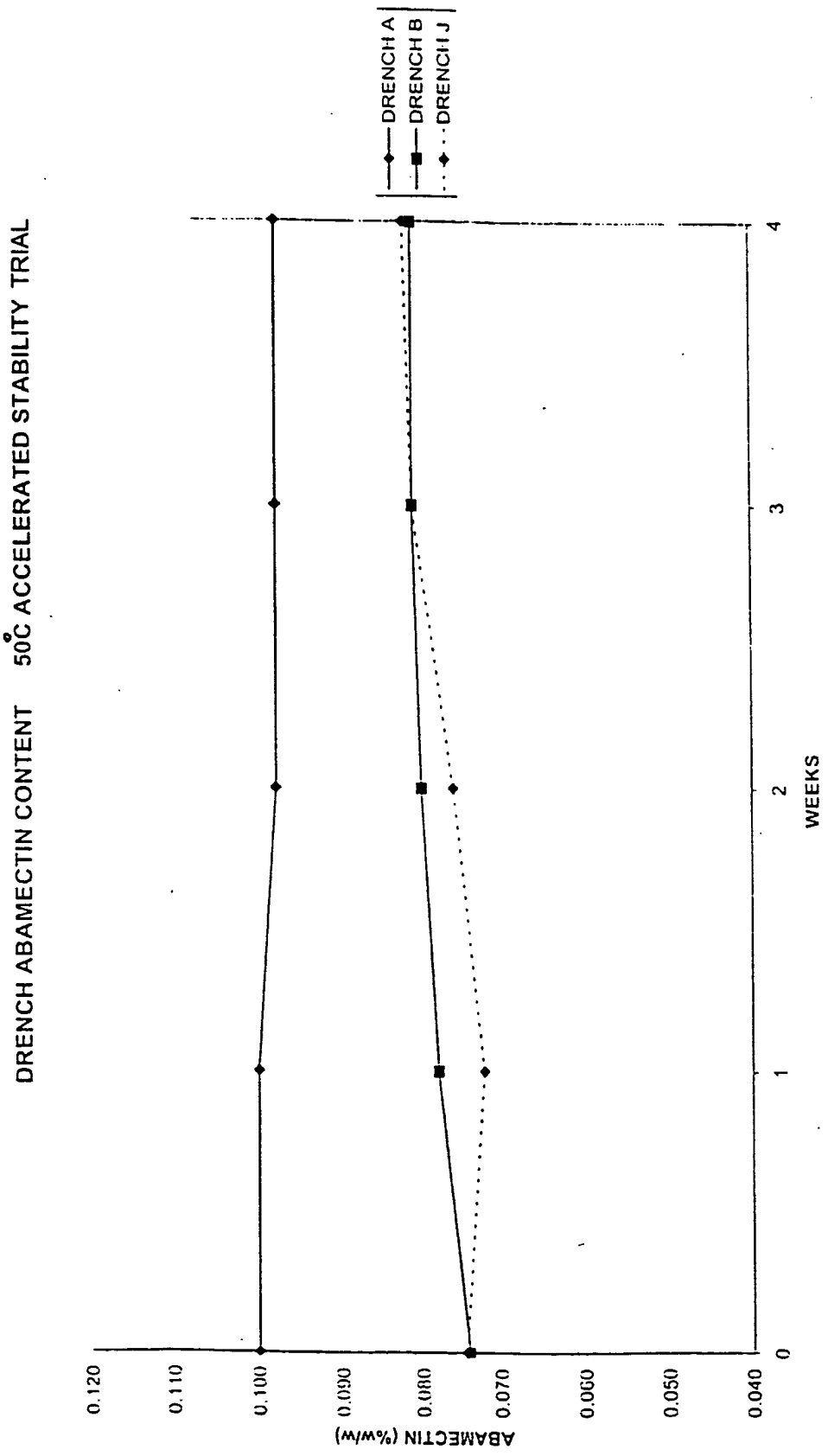

DRENCH ABAMECTIN CONTENT 50C ACCELERATED STABILITY TRIAL
DRENCH A
DRENCH B
DRENCH J
ABAMECTIN (%w/w)
0.120
0.110
0.100
0.090
0.080
0.070
0.060
0.050
0.040
WEEKS
0
1
2
3
4

FIGURE 25

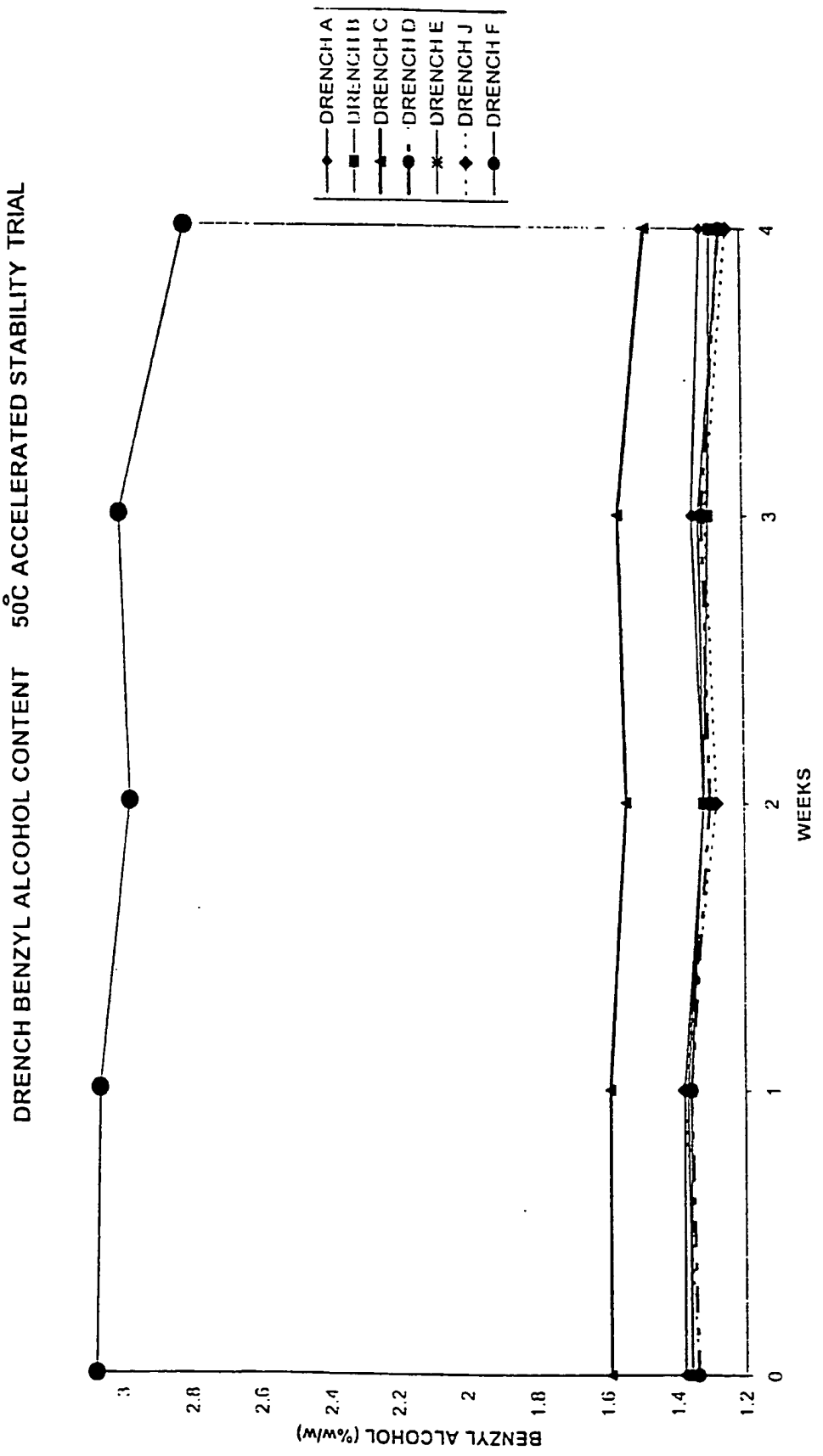

DRENCH BENZYL ALCOHOL CONTENT 50C ACCELERATED STABILITY TRIAL
DRENCH A
DRENCH B
DRENCH C
DRENCH D
DRENCH E
DRENCH J
DRENCH F
BENZYL ALCOHOL (%w/w)
2.8
2.6
2.4
2.2
2
1.8
1.6
1.4
1.2
0
1
2
3
4
WEEKS

FIGURE 26

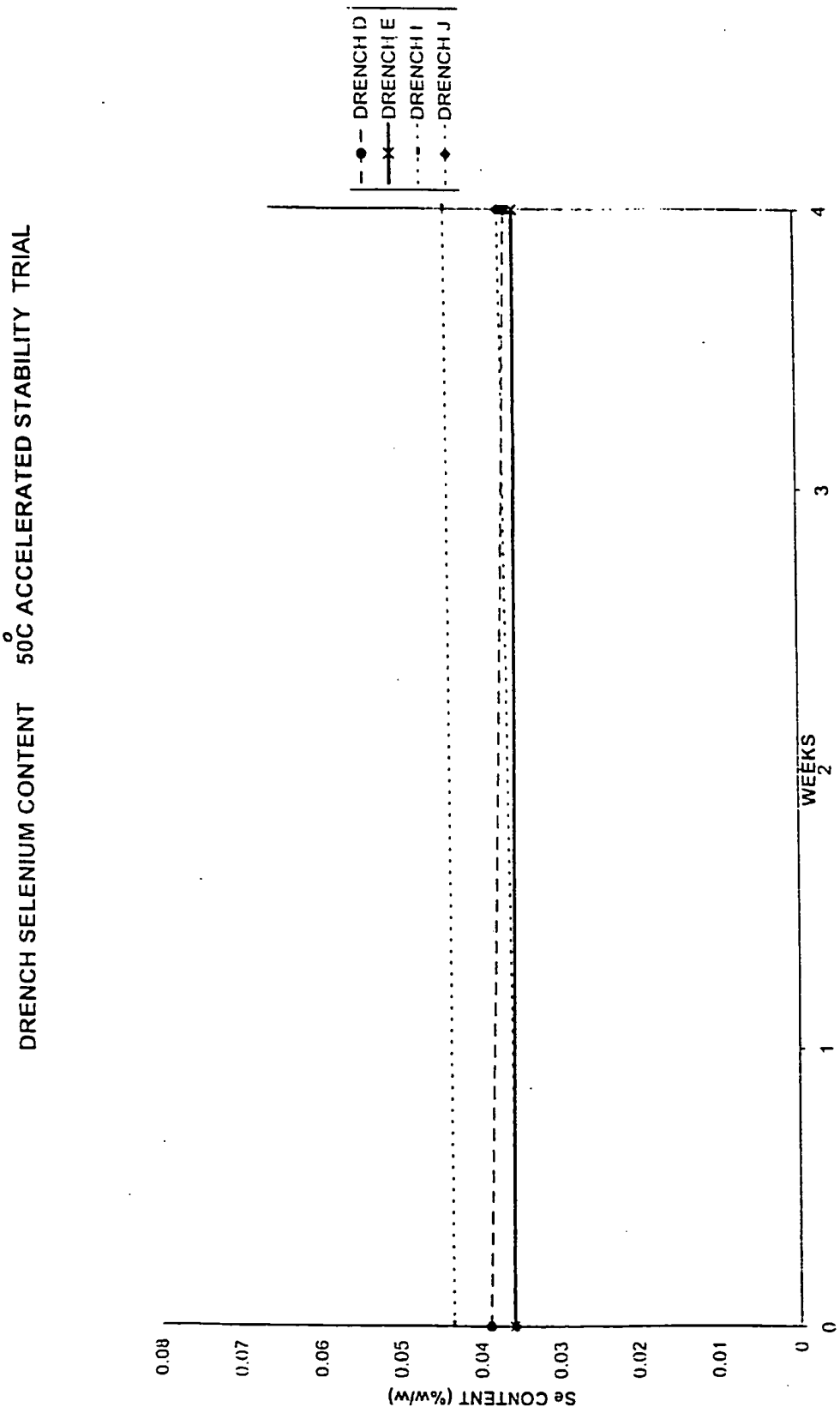

DRENCH SELENIUM CONTENT 50C ACCELERATED STABILITY TRIAL
DRENCH D
DRENCH E
DRENCH I
DRENCH J
Se CONTENT (%w/w)
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0
0
1
2
3
4
WEEKS

FIGURE 27

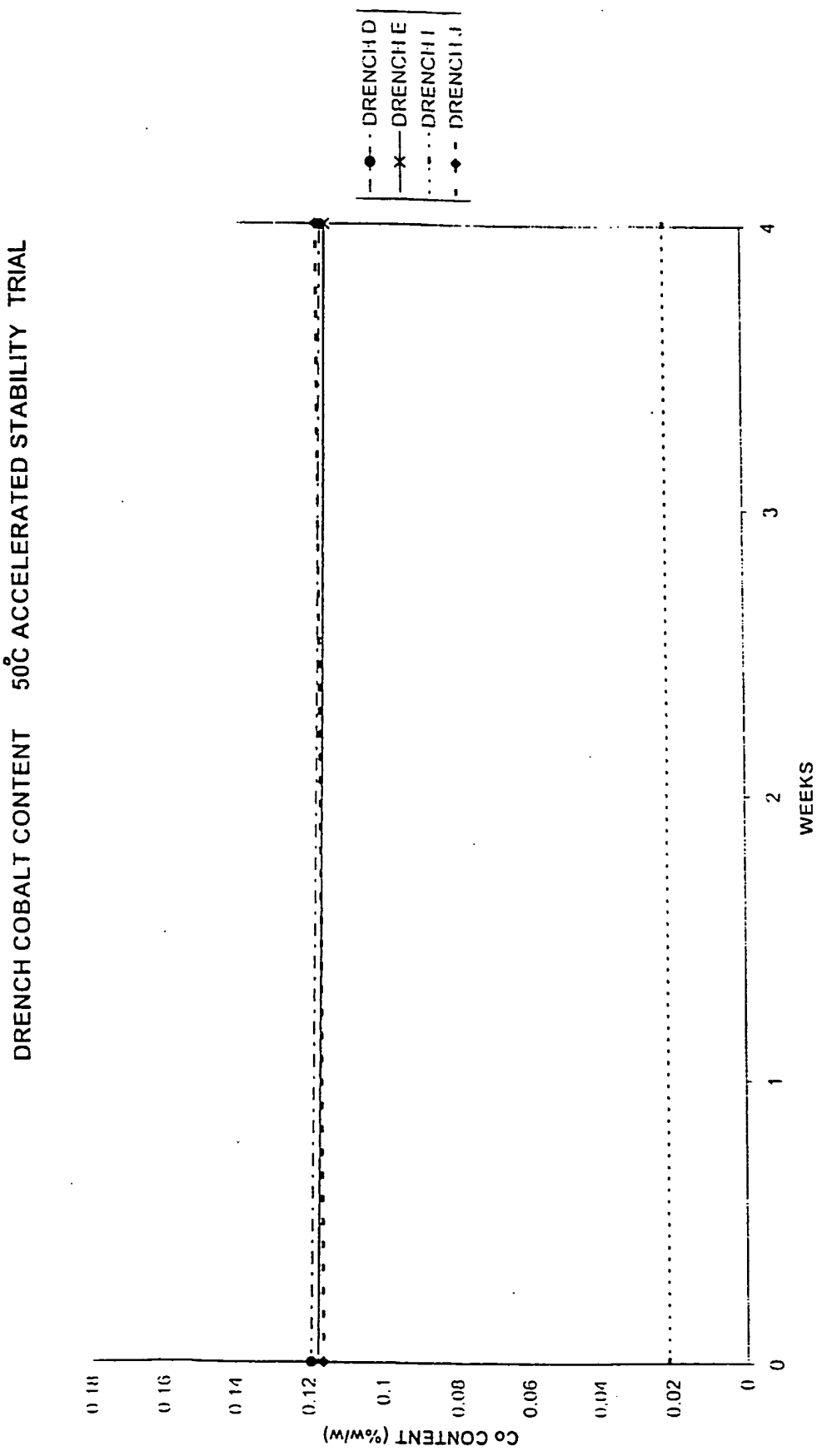

DRENCH COBALT CONTENT 50°C ACCELERATED STABILITY TRIAL
DRENCH D
DRENCH E
DRENCH I
DRENCH J
Co CONTENT (%w/w)
0.18
0.16
0.14
0.12
0.1
0.08
0.06
0.04
0.02
0
WEEKS
0
1
2
3
4

FIGURE 28

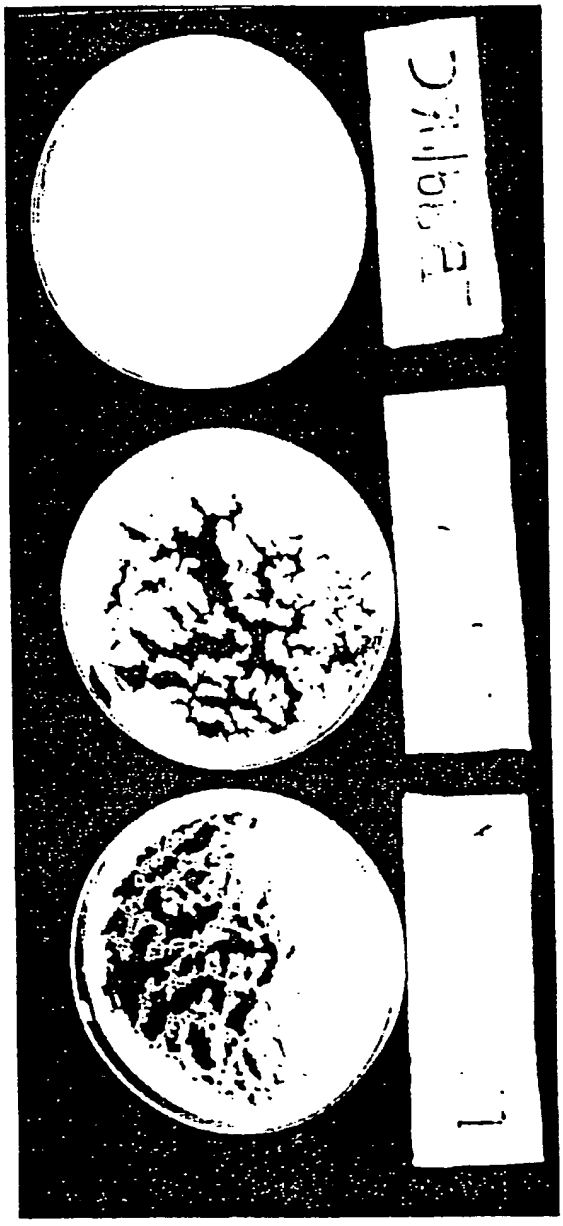

PARTICLES. Effect of Levamisole hydrochloride
(LB99/96C) on Clumping / Aggregation

FIGURE 29

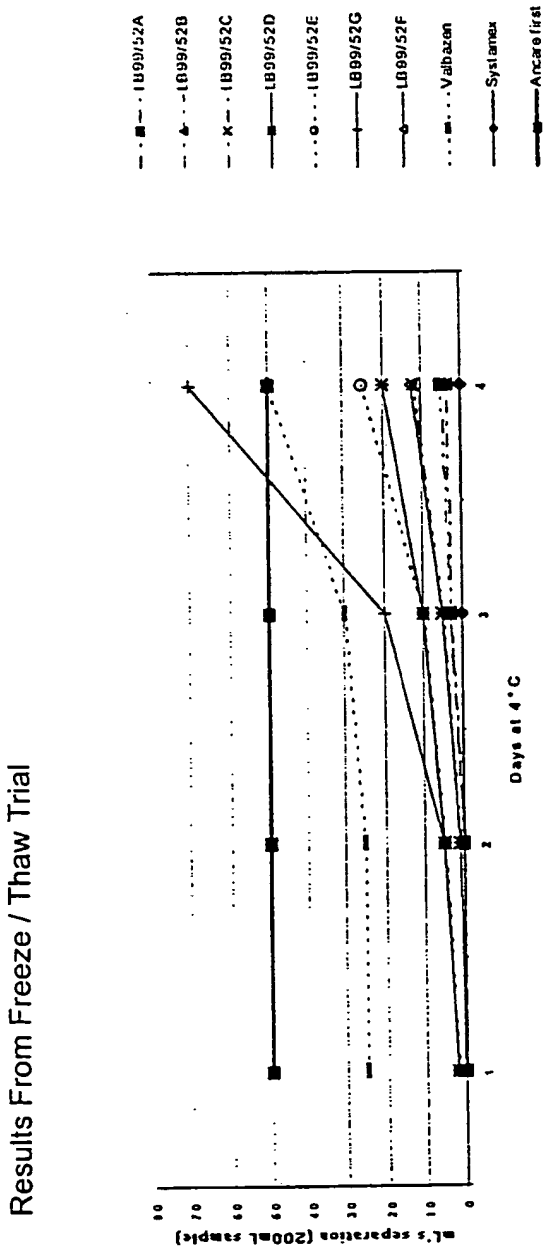

LB99/52A
LB99/52B
LB99/52C
LB99/52D
LB99/52E
LB99/52G
LB99/52F
Valbazen
Systamex
Ancare first
Results From Freeze / Thaw Trial
Days at 4°C
mL's separation (200mL sample)

FIGURE 30

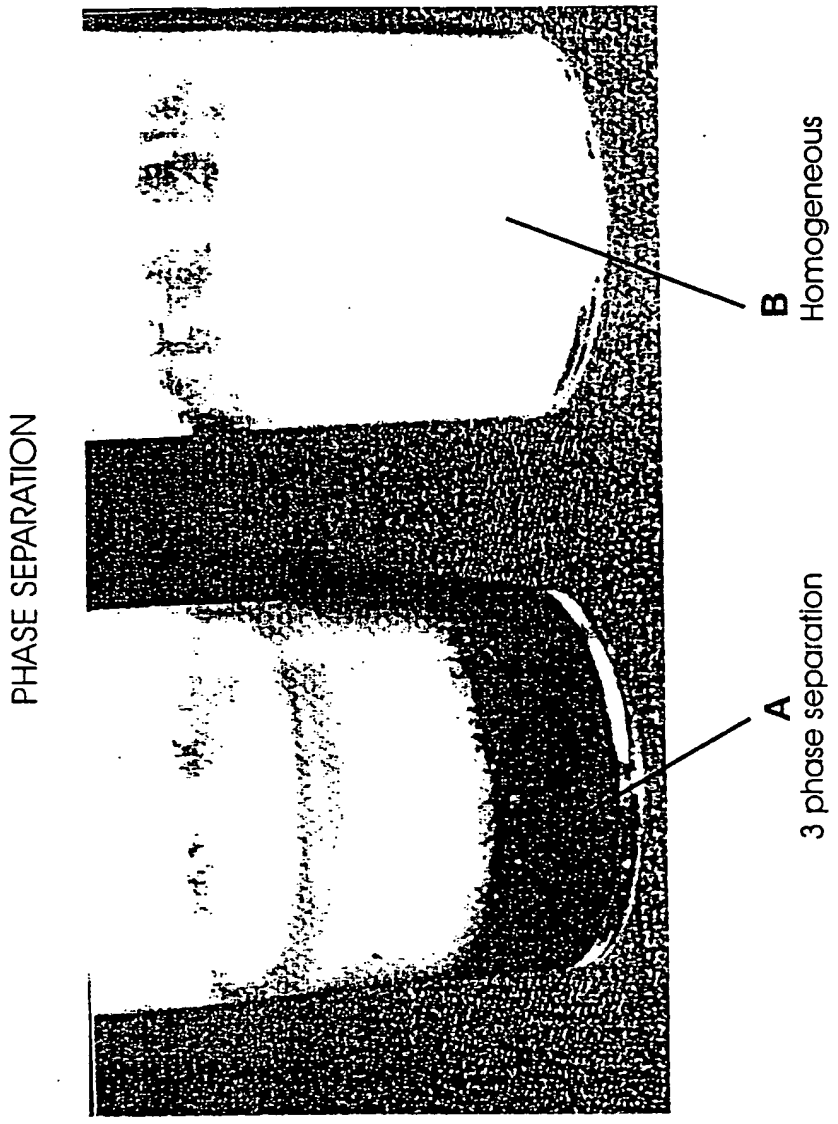


FIGURE 31

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NZ00/00087

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. [7]: A01N 43/90, 43/52, 25/02, A61K 31/4184, 31/429

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IC[7]:A01N 43/90, 43/52, 25/02, A61K 31/4184, 31/429
IC[6]: A61K 31/415, 31/425

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WPAT: levamisol#, tetramisol#, benzimidazol#,

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4395407 A (BALLANY *et al* .), 26 July 1983 - see whole document	1-16, 31-34, 39, 40, 44, 45, 52
X	US 3980791 A (SCHULZ *et al*), 14 September 1976 - see whole document	1-16, 31-34, 39, 40, 44, 45, 52
X	US 4278684 A (VAN DER VEKEN *et al*), 14 July 1981 - see whole document	1-16, 31-34, 39, 40, 44, 45, 52

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 October 2000	-6 NOV 2000

Name and mailing address of the ISA/AU

AUSTRALIAN PATENT OFFICE
PO BOX 200, WODEN ACT 2606, AUSTRALIA
E-mail address: pct@ipaustralia.gov.au
Facsimile No. (02) 6285 3929

Authorized officer

ISOBEL TYSON
Telephone No : (02) 6283 2563

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NZ00/00087

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 224249 A1 (SYNTEX (USA) INC), 3 June 1987 - see whole document	20-25, 44, 45, 49, 52
X	Derwent Abstract Accession No. 92-313277/38, Class P75, JP 04220398 A, (FUJI PHOTO FILM CO LTD) 11 August 1992 - see abstract	20-25, 44, 45, 49, 52
X	Derwent Abstract Accession No. 12122Y/07, Class B07 D14 E13, JP 52001046 A (OSHIO SANGYO KK) 6 January 1977 -see abstract	20-25, 44, 45, 49, 52
X	Derwent Abstract Accession No. 26659 K/11, Class B02 C02, JP 58021615 A (FUJISAWA PHARM KK) 8 February 1983 -see abstract	20-25, 44, 45, 49, 52
X	Derwent Abstract Accession No. 26424 K/11, Class Q31, JP 58020622 A, (OSHIO SANGYO KK) 7 February 1983 -see abstract	20-25, 44, 45, 49, 52
X	Derwent Abstract Accession No. 95-093720/13, Class C03 (C02), JP 07017812 A, (SHINTO TORYO KK) 20 January 1995 -see abstract	20-25, 44, 45, 49, 52
X	Derwent Abstract Accession No. 99081974/08, Class B02 C02, CN 1194832 A, (WANG Y) 7 October 1998 - see abstract	16

INTERNATIONAL SEARCH REPORT

International application No.
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Box I **Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos :

because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos : **17, 18, 19, 26-30, 35-38, 43, 44 (in part), 45 (in part), 46-48, 50, 51 and 52 (in part)**

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

The scope of these claims is so broad as to make a meaningful search not possible.

3. ☐ Claims Nos :

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box II **Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

(i) Claims 1-16, 31-34, 39, 40, 44 (in part), 45 (in part) and 52 (in part) are directed to compositions containing levamisole/tetramisole.
(ii) Claims 41 and 42 are directed to methods of formulating anthelmintic compositions.
(iii) Claims 20-25, 44 (in part), 45 (in part), 49 and 52 (in part) are directed to benzimidazole compositions.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims
2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/NZ00/00087

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
US	4395407	CA	1194791	GB	2098068	IE	52505
US	3980791	AU	69884/74	BE	816686	BR	7405115
		DE	2331793	FR	2233985	GB	1425810
		IE	39520	JP	5003542	LU	70356
		NL	7408296	SU	724077	ZA	7404001
US	4278684	AU	71322/81	CA	1157770	EP	42290
		IE	51329	NZ	197293	ZA	8104059
EP	224249	AU	65698/86	DK	5697/86	FI	864812
		HU	43575	IL	80767	JP	62155263
		NO	881787	NO	881788	PT	83812
		ZA	8608963	NO	874739		

END OF ANNEX

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